ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Effect of the Methanol Extract of *Haloxylon salicornicum* (Moq.) Bunge Ex Bioss. on Alleviating Inflammations.

Ibrahim M El-Ashmawy[1, 2]*, and Tariq I. Almundarij[1].

[1]Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Qassim University, P.O. Box 6622, Buraidah 51452, Saudi Arabia.
[2]Department of Pharmacology, Faculty of Veterinary Medicine, Alexandria University, Alexandria, Egypt.

ABSTRACT

Haloxylon salicornicum (*H. salicornicum*) is commonly used traditionally in treatment of inflammatory disorders. The aim of this study was to assess the effects of aerial parts of *H. salicornicum* against acute and sub-acute of inflammation in rat models. The models used were acute and sub-acute inflammations of rat paw induced by sub planter administration of carrageenan, and the granuloma- pouch bioassay at the dorsum of rats induced by turpentine oil. Additionally, the phytoconstituents of the studied extract was also investigated. *H. salicornicum* extracts significantly reduced inflammations in both phases acute model. Moreover, the activity in carrageenan induced sub-acute edema test in a dose-dependent manner. The methanolic extracts of *H. salicornicum* exhibited a significant reduction in exudate formation in granuloma-pouch bioassay. It could be concluded that the study verifies traditional use of *H. salicornicum* extracts for alleviating acute and sub-acute inflammatory disorders.

Keywords: *Haloxylon salicornicum*, Anti-Inflammatory, Carrageenan, Rat Paw Edema, Granuloma- Pouch Bioassay

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Inflammation is a biological defense response that is caused by harmful stimuli such as microbial infections and tissue injury. Physiologically, inflammation is beneficial event that leads organisms to expel harmful stimuli to initiate the restoration of tissue structure and function [1]. Currently, anti-inflammatory agents are the most frequently used drugs for medication, due to their wide range of therapeutic indications, including inflammation pain, edema, , rheumatoid arthritis , osteoarthritis, and skeletal muscle dysfunction [2]. Prolonged uses of these drugs are commonly induced severe side effects [3, 4].Consequently, alternative agents with limit side-effects are essential, and botanical products can be important candidates [5]. Thereby, there is a need to develop new anti-inflammatory agents with limited side effects [6].

Haloxylon salicornicum (Moq.) Bunge ex Bioss. is one of 120 genera and more than 1300 species belonging to the family Chenopodiaceae [7]. In Saudi Arabia, *H. salicornicum* and *H.persicum* are grown [8]. *H. salicornicum* known locally as Rimth and is widely separated all over the country. The phytochemical analysis of the aerial parts of *H. salicornicum* showed the presence of alkaloids, sterols, cardiac glycosides tannins, volatile bases and volatile oils [9]. And due to these bio-active properties, *H. salicornicum* was used in the treatment of diabetes [9] inflammations [10]; diarrhea [11, 12] and bacterial infection [13, 14]. Based on traditional use of *H. salicornicum* in treating inflammatory dysfunction, there is a need to investigate the influence of methanolic extract of aerial parts of *H. salicornicum* on different inflammatory models. In addition to that, the study was extended to determine its phytoconstituents.

MATERIALS AND METHOD

Animals

The study was performed using 50 Wistar albino mature male rats (180-200 g), were obtained from the College of pharmacy, Al-Qassim University, KSA. Rats were kept under standard conditions of temperature (22-26^{0}C), relative humidity (55-60), and fed a standard pellet diet with water *ad libitum*. The animals care and handling were in accordance with the world accepted standard guidelines. All animal procedures were approved by an institutional review board of Agricultural and Veterinary Medicine, AlQassim University, KSA.

Chemicals

Analytical grade chemicals were purchased from Sigma Aldrich, St. Louis, MO, USA and were used for the bioassays in the laboratory.

Methanol extracts preparation

The collected plant was air dried powdered (300 g) and soaked in methanol (3000 ml) with continuous shaking for 72 h. the methanol extract was filtered and the residues were re-percolated for three times. The extract was concentrated under reduced pressure. The obtained methanol extract was used for assaying its bioactivity and phytoconstituents. The Voucher specimen was deposited in the department of Botany, for further reference.

Determination of total phenolic and tannin contents

Total phenolic [15] and total tannins [16] of the methanol extracts of *H. salicornicum* were determined by using the Folin-Ciocalteu reagent. The values were expressed as gallic acid equivalents per g of extract.

Determination of total flavonoids

Total flavonoid content of the methanol extracts of *H. salicornicum* was determined by a colorimetric method of Zhishen et al. (1999) and calculated using a quercetin calibration curve. The results were expressed as quercetin equivalents per g of extract [17].

Anti-inflammatory models

Acute inflammatory model

The methods of Winter *et al*. [18] and Adeyemi *et al*. [19] were adopted. Rats were divided into five groups each of 5 animals. The first group was given only the vehicle (Carboxymethyl cellulose Na (CMC) 0.5%) and received as a control. Positive control group was treated with 20 mg/ kg diclofenac Na .Other three groups received respectively the methanol extracts of *H. salicornicum* at the dose levels 100, 200 and 400 mg/ kg b. wt. The methanol extract and diclofenac Na were suspended in 0.5% CMC and administered per os once every day with an oral gastric tube. Details of dose, time of administration and duration of treatment have been mentioned for each experimental paradigm studied.

One h after the administration of the compounds, carrageenan solution (0.1 ml of 1% w/v suspension in sterile 0.9% normal saline) was injected into the sub planter region of the hind paw. Immediately, the paw edema was measured Plethysmographically (Ugo Basile 7150, Varese, Italy Plethysmograph) before carrageenan injection. Thereafter the paw volume was measured after 1, 2 and 4 h from injection of carrageenan [18, 19]. The difference between the initial and following readings gave the change in edema volume for the corresponding time. The percentage of edema inhibition for each rat and each group was calculated according to the following equation:

$$\% \text{ inhibition} = \frac{(Vt - Vo)\ \text{control} - (Vt - Vo)\ \text{test compound}}{(Vt - Vo)\ \text{control}} \times 100$$

Where: Vt is the mean volume of edema at corresponding time interval and Vo is the mean volume of edema at zero time interval.

The model of sub-acute inflammation

Animals in the previous model were continued to take same treatments for seven successive days (the first group was given only the vehicle (carboxymethyl cellulose Na (CMC) 0.5%) and received as a control. Positive control group was treated with 20 mg/ kg diclofenac Na. Other three groups received respectively the methanol extracts of *H. salicornicum* at the dose levels 100.200 and 400 mg/ kg b. wt.). One h after the administration of the compounds, carrageenan solution was injected into the sub planter region of the hind paw and re-injected at the third day. The paw edema was measured plethysmographically at the 1^{st} and 8^{th} days [18, 19].

The dorsum granuloma pouch – inducion by turpentine oil

The method of Robert and Nezamis [20] was adopted and modified using turpentine oil as irritant [21]. In ether-anaesthetized rats subcutaneously dorsal granuloma pouch was made through injecting the amount of half ml of turpentine oil. As mentioned previously plant extracts given orally (at a doses level 100,200 and 400 mg/kg b. wt.) one h before the induction of granuloma and the administration of test materials continued daily for 7 days. On the 8^{th} day, all rats were anaesthetized with ether and the pouch exudates were collected. The exudate volume was measured for determining the anti-inflammatory activity of the tested materials as follows:

$$\text{Inhibition \%} = (V\ \text{control} - V\ \text{treated} / V\ \text{control} \times 100.$$

Statistical analysis

Data were analyzed using a one-way analysis of variance (ANOVA), $p \leq 0.05$. Once a significant difference was determined, the means were compared using Duncan, multiple range tests [22, 23].

RESULTS AND DISCUSSION

Inflammation is a biological protection mechanism. Acute inflammation is characterized by arteriole dilation, exudation of fluid, emigration of leukocytes from blood vessels to the area of damage and infected,

and release of inflammatory mediators and cytokines. While chronic inflammation is characterized by infiltration of mononuclear cells, proliferation of fibroblasts, blood vessels and elevatedconnective tissue formation [24]. Anti-inflammatory medications suppress different stages of inflammation [25].

The anti-inflammatory effect of methanol extract of aerial parts of *H. salicornicum* was assessed in different inflammatory models. Carrageenan- induces footpad edema in rats. Inhibition of carrageenan-induced inflammation in rats is one of the most valuable investigations to monitor anti-inflammatory properties of agents. [26]. Carrageenan, a mucopolysaccharide from Irish Sea moss Chondrus, is known to stimulate arthritis in lab animals. Additionally, it is non-immunogenic and does not activate systemic side effects [27]. Carrageenan activates the early phase of inflammation (1-2h) which is mediated by serotonin and histamine, and the late phase of inflammation (after 2nd h) which is sustained by prostaglandins and formation of bradykinin [28-30]. These mediators confer inflammatory response and pain. It has been shown that the second phase of carrageenan-induced edema is sensitive to clinically used anti-inflammatory drugs and commonly employed to evaluate the anti- phlogistic effect of the natural products [31, 32].

In the present study, the plant extracts of *H. salicornicum* showed anti-inflammatory activity in the both phases of carrageenan induced acute edema test in a dose-dependent manner (Table 1). Moreover, the strongest activity of these extracts was arranged in a dose dependent manner against carrageenan induced sub-acute edema test also in a dose-dependent manner (Table 2). Likewise, NSAID drug diclofenac sodium produced significant ($p<0.05$) anti-edematous effect which is consistent with the previous reports [33-35]. Multiple studies have shown that the inhibitory effects of plant extracts and NSAIDs in similar animal models of pain and inflammation [36-39]. It is known that diclofenac and aspirin inhibit inflammation and pain by attenuating prostaglandin synthesis via cyclooxygenase inhibition in arachidonic acid pathways [33].

Table 1: Influence of the methanol extract of *Haloxylon salicornicum* against carrageenan–induced acute type of inflammation

Treatment	Paw edema volume (mL)			
	0	1h	2h	4h
Control (Vehicle)	1.12±0.01	2.76±0.01	3.60±0.03	3.84±0.02
H. salicornicum (100 mg/kg)	1.10±0.01	1.73±0.03(37) *	2.48±0.04(31) *	2.61±0.02(32) *
H. salicornicum (200 mg/kg)	1.14±0.01	1.74±0.03(37) *	2.36±0.05(34) *	2.55±0.04(33) *
H. salicornicum (400 mg/kg)	1.11±0.01	1.61±0.01(41) *	2.22±0.02(38) *	2.44±0.01(36) *
Diclofenac Na (20 mg/kg)	1.13±0.02	1.68±0.12(39) *	2.26±0.03(37) *	2.42±0.03(37) *

*Values are expressed as mean ± S.E. P≤0.05. Number of animals = 5.

Table 2: Influence of the methanol extract of *Haloxylon salicornicum* against carrageenan –induced sub-acute type of inflammation

Treatment	Paw edema volume (mL)		
	0 day	1st day	8th day
Control (Vehicle)	1.12±0.01	3.84±0.02	5.55±0.12
H. salicornicum(100 mg/kg)	1.10±0.01	2.61±0.02(32) *	4.66±0.13(15) *
H. salicornicum(200 mg/kg)	1.14±0.01	2.55±0.04(33) *	4.36±0.10(21) *

H. salicornicum(400 mg/kg)	1.11±0.01	2.44±0.01(36) *	3.46±0.20(37) *
Diclofenac Na (20 mg/kg)	1.13±0.02	2.42±0.03(37) *	3.53±0.15(36) *

*Values are expressed as mean ± S.E. P≤0.05. Number of animals = 5.

Table 3: Anti-inflammatory Efficacy of the Methanol Extracts of *Haloxylon salicornicum* on the granuloma pouch model –induced by turpentine oil

Treatment	Exudates volume	Inhibition %
Control (Vehicle)	2.14±0.02	------
H. salicornicum (100 mg/kg)	1.79±0.01*	16
H. salicornicum(200 mg/kg)	1.69±0.01*	21
H. salicornicum(400 mg/kg)	1.43±0.02*	33
Diclofenac Na (20 mg/kg)	1.32±0.02*	39

*Values are expressed as mean ± S.E. P≤0.05. Number of animals = 5.

Table 4: Quantitative phytoconstituents of the methanol extract of *Haloxylon salicornicum*.

	Quantitative analysis (mg/g of methanolic residue)			
	Total phenolic	Tannins	Non tannins	Total flavonoids
H. salicornicum	60.52	13.85	46.67	58.1

Turpentine oil can be used as an irritant. Therefore, turpentine oil-induced granuloma pouch offer a model for exudative type of inflammation. This model is a widely used model for chronic inflammation which occurs by means of development of proliferated cells in the form of granuloma. Inflammation involves proliferation of macrophages, neutrophils and fibroblasts, which are basic sources of granuloma formation [40] . In the present study, the results depicted in (Table 3) revealed that, the plant extract of *H. salichornicum* exhibited potential inhibitory action on exudate formation. Kinin is the main mediator of granuloma, as it both vasodilate and increase vascular permeability in the early stages of inflammation [41]. Keeping all these in view, it may be said that the tested plant extracts may possess anti-kinin like activity. The test plant extracts inhibit the granuloma formation by inhibiting granulocyte infiltration, generation of collagen fibers, fibroblasts and suppressing mucopolysaccharides [42]. A collective interpretation of the anti-inflammatory data of the test plant extracts (Tables 1-3) revealed that *H. salichornicum* demonstrated pronounced activities in the three animal models used in this study and the effect was equal in strength to that of the diclofenac sodium.

The tested plant extracts found to possess high concentrations of tannins, polyphenols and flavonoids (Table 4). These phytoconstituents could be responsible for anti-inflammatory activity [43-45]. It has been shown that, flavonoids suppress the enzyme prostaglandin synthetase, specifically the end peroxidase resulting a significant anti-inflammatory activity due to inhibition of chemical mediators of inflammation [46, 47]. COX-1 and COX-2 catalyze the biosynthesis of prostaglandin H2 from the arachidonic acid substrate. The inhibition of COX-1 results in some undesirable side-effects, while COX-2 inhibition provides therapeutic effects in pain, inflammation, glaucoma, cancer, Alzheimer‘s and Parkinson disease [48]. Similarly, phenolic compounds showed high anti-inflammatory activity [49, 50]. Many polyphenolics, tannins and flavonoids have been found to inhibit COX-1 and COX-2 [51-54]. The anti-inflammatory effect of extract may, therefore, be due to the presence of flavonoids and tannins.

CONCLUSION

It is concluded that methanolic extract of *Haloxylon salichornicum* possesses potential anti-inflammatory activity, which is analogous to diclofenac sodium. The study also signifies that phytoconstituents

(total phenols and flavonoids) could be responsible, at least in part, for its anti-inflammatory activity. The study confirms the potency of this plant extracts for alleviating inflammation.

REFERENCES

[1] Ricciotti, E. and G.A. FitzGerald, Prostaglandins and Inflammation. Arterioscler Thromb Vasc Biol, 2011. 31(5): p. 986-1000.

[2] Al-Saeed, A., Gastrointestinal and Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs, in Oman Med J. 2011. p. 385-91.

[3] Miller, T.A., Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am J Physiol, 1983. 245(5 Pt 1): p. G601-23.

[4] Yuan, Y., I.T. Padol, and R.H. Hunt, Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol, 2006. 3(2): p. 80-9.

[5] Verpoorte, R., Exploration of nature's chemodiversity: the role of secondary metabolites as leads in drug development. Drug Discovery Today, 1998. 3(5): p. 232-238.

[6] Vane, J. and R. Botting, Inflammation and the mechanism of action of anti-inflammatory drugs. Faseb j, 1987. 1(2): p. 89-96.

[7] Ghazanfar, S.A., Handbook of Arabian medicinal plants. 1994: CRC press.

[8] Shaukat, A., Flora of the Kingdom of Saudi Arabia Illustrsated. Vol. I, Ministry of Agriculture and Water, Riyadh, Saudi Arabia, 2000: p. 180-181.

[9] Ajabnoor, M.A., et al., Antidiabetic activity of Hammada salicornica. Fitoterapia, 1984. 55: p. 107–109.

[10] Al-Shanawani, M., Plant used in Saudi folk medicine. King Abdul-Aziz city for Science and Technology (KACST), Riyadh, Saudi Arabia, 1996: p. 162.

[11] Al Harbi, K.B. and I.M. El-Ashmawy, The antidiarrheal activity and phytoconstituents of some methanol extracts from Asteraceae family. Merit Res J Med Med Sci, 2015. 3(8): p. 347-52.

[12] Al-Harbi, K.B., I.M. El-Ashmawy, and N.A. Al-Wabel, The antidiarrheal activity of the methanol extract of some plants native to Al-Qassim Region, Saudi Arabia. Journal of Food, Agriculture & Environment, 2016. 14(2): p. 239.

[13] Aldoweriej, A.M., et al., Antimicrobial activity of various extracts from some plants native to Alqassim Region, Saudi Arabia. Journal of Food, Agriculture & Environment, 2016. 14(1): p. 14-19.

[14] Al-Saeed, A., Study the effect of some extracts of Haloxylon sp. on blood glucose level in normal and hyperglycemic rabbits induced by alloxan. 2002, M. Sc. Thesis, College of Science-University of Basrah.

[15] Singleton, V.L. and J.A. Rossi, Colorimetry of Total Phenolics with Phosphomolybdic-Phosphotungstic Acid Reagents. 1965.

[16] Osoro, K., et al., Anthelmintic and nutritional effects of heather supplementation on Cashmere goats grazing perennial ryegrass-white clover pastures. J Anim Sci, 2007. 85(3): p. 861-70.

[17] Zhishen, J., T. Mengcheng, and W. Jianming, The determination of flavonoid contents in mulberry and their scavenging effects on superoxide radicals. Food chemistry, 1999. 64(4): p. 555-559.

[18] Winter, C.A., E.A. Risley, and G.W. Nuss, Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. Proc Soc Exp Biol Med, 1962. 111: p. 544-7.

[19] Adeyemi, O., S. Okpo, and O. Ogunti, Analgesic and anti-inflammatory effects of the aqueous extract of leaves of Persea americana Mill (Lauraceae). Fitoterapia, 2002. 73(5): p. 375-380.

[20] Robert, A. and J.E. Nezamis, The granuloma pouch as a routine assay for antiphlogistic compounds. Acta Endocrinol (Copenh), 1957. 25(1): p. 105-12.

[21] Shastry, V., V. Patil, and R. Chaudhari, Acute and chronic anti-inflammatory activity of Pergularia daemia whole plant in various experimental animal models. Int J Pharm Pharm Sci, 2011. 3(3).

[22] Duncan, D.B., Multiple Range and Multiple F Tests. Biometrics, 1955. 11(1): p. 1-42.

[23] Schlotzhauer, S.D. and R.C. Littell, SAS system for elementary statistical analysis. 1997: SAS institute Cary, North Carolina.

[24] Gryglewski, R.J., Molecular mechanisms of inflammation. Eur J Rheumatol Inflamm, 1981. 4(2): p. 153-9.

[25] Benni, J.M., M.K. Jayanthi, and R.N. Suresha, Evaluation of the anti-inflammatory activity of Aegle marmelos (Bilwa) root. Indian J Pharmacol, 2011. 43(4): p. 393-7.

[26] Di Rosa, M., J.P. Giroud, and D.A. Willoughby, Studies on the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. J Pathol, 1971. 104(1): p. 15-29.

[27] Vinegar, R., et al., Pathway of onset, development, and decay of carrageenan pleurisy in the rat. Fed Proc, 1982. 41(9): p. 2588-95.

[28] Georgewill, O., U. Georgewill, and R. Nwankwoala, Anti-inflammatory effects of Morninga oleifera lam extract in rats. Asian Pacific Journal of Tropical Medicine, 2010. 3(2): p. 133-135.
[29] Vinegar, R., W. Schreiber, and R. Hugo, Biphasic development of carrageenin edema in rats. J Pharmacol Exp Ther, 1969. 166(1): p. 96-103.
[30] Mohan, V., ANTI-INFLAMMATORY ACTIVITY OF LEAF OF MELASTOMA MALABATHRICUM. Vol. 3. 2012. 801-802.
[31] Riaz, N., et al., Cholinesterase-inhibiting withanolides from Ajuga bracteosa. Chem Biodivers, 2004. 1(9): p. 1289-95.
[32] Riaz, N., et al., Isolation and Enzyme-Inhibition Studies of the Chemical Constituents from Ajuga bracteosa. Chemistry & biodiversity, 2007. 4(1): p. 72-83.
[33] Vane, J.R., Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol, 1971. 231(25): p. 232-5.
[34] Gautam, R., et al., Anti-inflammatory, cyclooxygenase (COX)-2, COX-1 inhibitory and antioxidant effects of Dysophylla stellata Benth. Fitoterapia, 2010. 81(1): p. 45-9.
[35] Gautam, R., et al., Anti-inflammatory, cyclooxygenase (COX)-2, COX-1 inhibitory, and free radical scavenging effects of Rumex nepalensis. Planta Med, 2010. 76(14): p. 1564-9.
[36] Lavrenova, G. and I.P. Chernov, [Comparative evaluation of the effect of plant polysaccharides on the inflammatory process and regeneration in chronic stomach ulcer]. Farmakol Toksikol, 1983. 46(4): p. 85-9.
[37] Hernandez, I., et al., Anti-inflammatory effects of ethanolic extract and alkamides-derived from Heliopsis longipes roots. J Ethnopharmacol, 2009. 124(3): p. 649-52.
[38] Boller, S., et al., Anti-inflammatory effect of crude extract and isolated compounds from Baccharis illinita DC in acute skin inflammation. J Ethnopharmacol, 2010. 130(2): p. 262-6.
[39] Chagas-Paula, D.A., et al., Outstanding Anti-inflammatory Potential of Selected Asteraceae Species through the Potent Dual Inhibition of Cyclooxygenase-1 and 5-Lipoxygenase. Planta Med, 2015. 81(14): p. 1296-307.
[40] Arul, B., et al., Anti-inflammatory activity of Coldenia procumbens Linn. Pak J Pharm Sci, 2005. 18(3): p. 17-20.
[41] Banerjee, S., et al., 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(1): p. 21-24.
[42] Dikshit, A., V. Gauttam, and A.N. Kalia, Evaluation of Anti-inflammatory activity of Methanolic extract of Cassia obtusifolia seeds in Wistar rats. J. Chem. Pharm. Res 2010; 2 (5): 696, 2010. 700.
[43] Nijveldt, R.J., et al., Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr, 2001. 74(4): p. 418-25.
[44] Havsteen, B.H., The biochemistry and medical significance of the flavonoids. Pharmacol Ther, 2002. 96(2-3): p. 67-202.
[45] Chhabra, G. and K. Kulkarni, Evaluation of anti-inflammatory activity of Vitex agnus castus leaves. Quantitative analysis of flavonoids as possible active constituents. Journal of Pharmacognosy and Phytochemistry, 2014. 3(1): p. 183-189.
[46] Serafini, M., I. Peluso, and A. Raguzzini, Flavonoids as anti-inflammatory agents. Proc Nutr Soc, 2010. 69(3): p. 273-8.
[47] Hussain, L., et al., Analgesic, anti-inflammatory and antipyretic activity of Salvia moorcroftiana. Pakistan Journal of Pharmaceutical Sciences, 2017. 30(2).
[48] Blobaum, A.L. and L.J. Marnett, Structural and functional basis of cyclooxygenase inhibition. J Med Chem, 2007. 50(7): p. 1425-41.
[49] Ahmadiani, A., et al., Antinociceptive and anti-inflammatory effects of Elaeagnus angustifolia fruit extract. J Ethnopharmacol, 2000. 72(1-2): p. 287-92.
[50] Parveen, Z., et al., Antiinflammatory and analgesic activities of Thesium chinense Turcz extracts and its major flavonoids, kaempferol and kaempferol-3-O-glucoside. Yakugaku Zasshi, 2007. 127(8): p. 1275-9.
[51] Haqqi, T.M., et al., Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. Proceedings of the National Academy of Sciences, 1999. 96(8): p. 4524-4529.
[52] Albert, D., et al., Hyperforin is a dual inhibitor of cyclooxygenase-1 and 5-lipoxygenase. Biochem Pharmacol, 2002. 64(12): p. 1767-75.
[53] O'Leary, K.A., et al., Effect of flavonoids and vitamin E on cyclooxygenase-2 (COX-2) transcription. Mutat Res, 2004. 551(1-2): p. 245-54.
[54] Beg, S., et al., Systematic review of herbals as potential anti-inflammatory agents: Recent advances, current clinical status and future perspectives, in Pharmacogn Rev. 2011. p. 120-37.