Research & Reviews: Journal of Medicinal & Organic Chemistry

Non-Steroidal Anti Inflammatory Drugs- A Systematic Review

B.Revathi
[1]Department of Pharmaceutical Chemistry, Osmania University, Hyderabad

Review Article

Received date: 28/04/2015
Accepted date: 29/04/2015
Published date: 01/05/2015

***For Correspondence**

Revathi.B, M.Pharm, Pharmaceutical Chemistry, Osmania University, Hyderabad, Telangana, India, Tel: 91-9533484346;

E-mail: revz.pharm@gmail.com

Keywords: Inflammation, Non-steroidal, Analgesic, Prostaglandins, Inhibitors.

ABSTRACT

Inflammtion can be well understood by its symptoms. The most common anti-inflammatory drug used is Aspirin. Gradually many anti-inflammatory drugs wer discovered. All these were put under non-steroidal class for anti-inflammatory drugs. They possess certain general charecteristics in terms of mechanism, adverse effects, therapeutic uses etc. which has been discussed in a systematic manner. The claases of NSAIDs is discussed with examples.

INTRODUCTION

Inflammation

Inflammation may be defined as the series of changes that occur in living tissues following injury. Injury may be caused due to various exogenous and endogenous stimuli, which in turn initiate protective response in the host cell [1-3].

The signs of inflammation are:

1. Rubor (Redness)
2. Tumor (Swelling)
3. Calor (Heat)
4. Dolor (Pain)
5. Futio leasa (Loss of functional activities).

The term non-steroidal anti-inflammatory drugs, in short NSAIDs, encompass all the heterogeneous group of compounds that possess analgesic, antipyretic (lowers elevated body temperature) and also anti-inflammatory properties [6-10]. The exception to this is Paracetamol and certain other drugs which are devoid of anti-inflammatory actions. The NSAIDs are also termed non-narcotic analgesic agents. However, the analgesic action produced by these agents is of relatively low degree than opiod analgesics.

Aspirin, is the prototype drug of NSAIDs. NSAIDs have attained the status of being the most commonly used OTC drugs. The traditional or conventional NSAIDs are liable to precipitate adverse gastrointestinal effects [11].

Almost three decades ago, steroids namely: prednisolone, dexamethasone, bethamethasone, triamcinoline and hydrocortisone were considered to be the drug of choice as anti-inflammatory agents. Owing to the several adverse effects caused by either short-term or long-term steroid therapy, these have been more or less replaced by much safer and better tolerated nonsteroidal anti inflammatory drugs (NSAIDs).

The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since he past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting therapeutic efficacy accompanied with fewer untoward reactions [12-14].

General characteristic features of NSAIDs

1. They are non-steroidal compounds i.e., devoid of steroidal ring in their basic skeleton.
2. They possess analgesic, antipyretic and anti-inflammatory actions.
3. These NSAIDs are also termed non-narcotic, non-opioid analgesics as they do not interact with opioid receptors.
4. They do not produce CNS and respiratory depression, dependence, sleep etc., which are the characteristic features of opioid analgesics.
5. These drugs exert their therapeutic response by exerting an inhibitory effect on cyclo-oxygenases (COX-1 and COX-2), thereby inhibiting the generation of certain inflammatory prostaglandins (PGs).

General mechanism of action of NSAIDs

NSAIDs are potent inhibitors of cycloxygenases enzymes (2 isoforms-COX1 and COX2). The non-selective NSAIDs inhibit both the isoforms, while the selective COX2 NSAIDs are inhibitors of COX2 enzyme only.

Arachidonic acid is released from the membrane phospholipids in response to disturbances of the cell membrane. This arachidonic acid undergoes metabolism to form various eicosanoids by four different pathways, only cycloxygenase and lipoxygenase pathways are discussed here as the COX enzymes involved in this pathway are the major target for NSAIDs [15].

Prostaglandins and also thromboxane's so generated act as potent mediators of inflammation. Inflammation is brought about by inducing vasodilation of vasculature, increasing the vascular permeability and also by sensitization of nociceptive receptors (PGE2).

NSAIDs exert their effect by inhibiting the enzyme cycloxygenases, due to which the arachidonic acid cascade gets precluded. Such inhibition is effected by binding of drugs to the amino acid arginine, located at position 120 on the target, i.e., cycloxygenases enzyme. The prototype NSAID i.e., aspirin and its congeners are irreversible inhibitors of COX enzyme. The non-selective COX inhibitors get bound at position 120 of both COX1 and COX2 hence are termed non selective in action. Inhibition on COX1 results in analgesic and antipyretic activity, while inhibition of COX2 results in anti-inflammatory activity [16,17].

General adverse effects of NSAIDs

a) Gastro intestinal manifestations
b) Renal manifestations
c) Renal manifestations
d) CNS manifestations
e) Hepatic manifestations
f) Hypersensitive reactions

General therapeutic uses of NSAIDs

a) Analgesics- reduction of pain
b) Antipyretics- lowering of body temperature when this is raised in disease (i.e. fever).
c) Anti-inflammatory agents- modification of the inflammatory reaction

CLASSIFICATION

NSAIDs may be classified on the basis of their basic chemical structures.

a) Hetero aryl acetic acid analogues
b) Aryl propionic acid analogues

c) Aryl acetic acid analogues

d) Naphthalene acetic acid analogues

e) Gold compounds

The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of non-steroidal anti-inflammatory drugs since he past three decades. A good number of these agents have been put into clinical usage widely and confidently thereby exhibiting therapeutic efficacy accompanied with fewer untoward reactions [12-14].

General characteristic features of NSAIDs

1. They are non-steroidal compounds i.e., devoid of steroidal ring in their basic skeleton.
2. They possess analgesic, antipyretic and anti-inflammatory actions.
3. These NSAIDs are also termed non-narcotic, non-opioid analgesics as they do not interact with opioid receptors.
4. They do not produce CNS and respiratory depression, dependence, sleep etc., which are the characteristic features of opioid analgesics.
5. These drugs exert their therapeutic response by exerting an inhibitory effect on cyclo-oxygenases (COX-1 and COX-2), thereby inhibiting the generation of certain inflammatory prostaglandins (PGs).

General mechanism of action of NSAIDs

NSAIDs are potent inhibitors of cycloxygenases enzymes (2 isoforms-COX1 and COX2). The non-selective NSAIDs inhibit both the isoforms, while the selective COX2 NSAIDs are inhibitors of COX2 enzyme only.

Arachidonic acid is released from the membrane phospholipids in response to disturbances of the cell membrane. This arachidonic acid undergoes metabolism to form various eicosanoids by four different pathways, only cycloxygenase and lipoxygenase pathways are discussed here as the COX enzymes involved in this pathway are the major target for NSAIDs [15].

Prostaglandins and also thromboxane's so generated act as potent mediators of inflammation. Inflammation is brought about by inducing vasodilation of vasculature, increasing the vascular permeability and also by sensitization of nociceptive receptors (PGE2).

NSAIDs exert their effect by inhibiting the enzyme cycloxygenases, due to which the arachidonic acid cascade gets precluded. Such inhibition is effected by binding of drugs to the amino acid arginine, located at position 120 on the target, i.e., cycloxygenases enzyme. The prototype NSAID i.e., aspirin and its congeners are irreversible inhibitors of COX enzyme. The non-selective COX inhibitors get bound at position 120 of both COX1 and COX2 hence are termed non selective in action. Inhibition on COX1 results in analgesic and antipyretic activity, while inhibition of COX2 results in anti-inflammatory activity [16,17].

General adverse effects of NSAIDs

a) Gastro intestinal manifestations

b) Renal manifestations

c) Renal manifestations

d) CNS manifestations

e) Hepatic manifestations

f) Hypersensitive reactions

General therapeutic uses of NSAIDs

a) Analgesics- reduction of pain

b) Antipyretics- lowering of body temperature when this is raised in disease (i.e. fever).

c) Anti-inflammatory agents- modification of the inflammatory reaction

CLASSIFICATION

NSAIDs may be classified on the basis of their basic chemical structures.

a) Hetero aryl acetic acid analogues

b) Aryl propionic acid analogues

c) Aryl acetic acid analogues

d) Naphthalene acetic acid analogues

e) Gold compounds

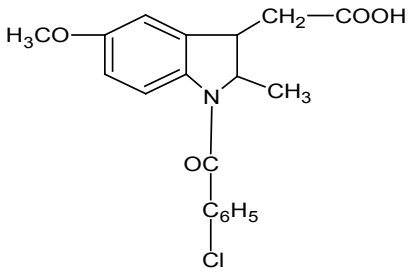
f) Misc. anti-inflammatory drugs

g) Salicylic acid analogues

h) Pyrazolones and pyrazolodiones

Hetero aryl acetic acid analogues

This constitutes an important class of NSAIDs which have gained importance in the recent past. A few classical examples of this group are, Indomethacin; sulindac; tolmetin sodium; zomepirac sodium [18]. Eg: Indomethacin (Figure 1). Indomethacin is a non-steroid drug possessing anti-inflammatory, anti-pyretic and analgesic properties. It is usually sued for the treatment of rheumatoid arthritis, spondylitis, gouty arthritis and osteoarthritis [19]. It is not an ordinary simple analgesic and owing to its reasonably serious untoward effects should be used with great caution.

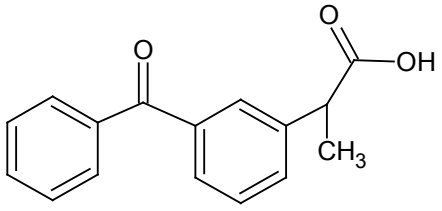


[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]aceticacid

Figure 1: Indomethacin.

Aryl propionic acid analogues:

These analogues exhibit potent anti-inflammatory properties besides usual antipyretic and analgesic characteristics [20]. A few examples of this category of compounds are flurbiprofen, ketoprofen, indoprofen, fenoprofen calcium. Eg: Ketoprofen (Figure 2). It acts by inhibiting the synthesis of leukotriens and their migration to inflamed joints [21]. It is used in the treatment of rheumatoid arthritis and osteoarthritis.

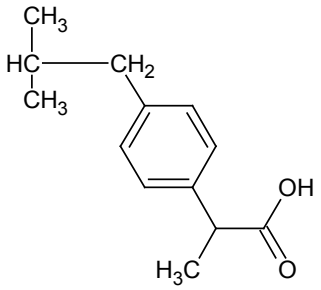


2-[3-(phenylcarbonyl)phenyl]propanoic acid

Figure 2: Ketoprofen.

Aryl acetic acid analogues

Eg: Ibuprofen (Figure 3).

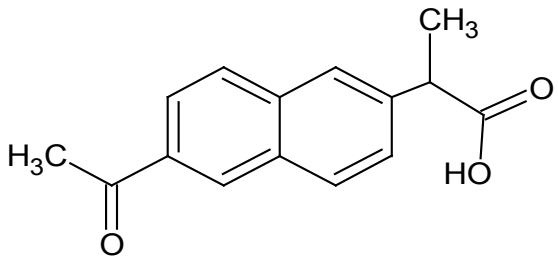


2-[4-(2-methylpropyl)phenyl]propanoic acid

Figure 3: Ibuprofen.

Napthalene acetic acid analogues

The recent intensive quest for NSAIDs and aryl acetic acids in particular offer a brighter scope that the naphthalene acetic acid analogues might turn out to be the leading compounds of an extensive series of promising clinical agents [22-26]. Eg: Naproxen (Figure 4).



2-(6-acetylnaphthalen-2-yl)propanoic acid

Figure 4: Naproxen.

Miscellaneous Anti-Inflammatory Drugs

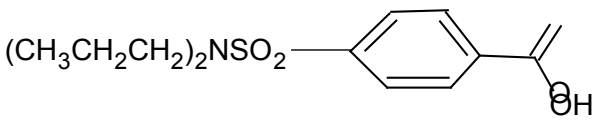
Antimalarial Agents

Chloroquine and hydroxyl chloroquine belonging to the class of 4-amino-quinoline antimalarials are ebing used in clinical practice in the cure and treatment of rheumatoid arthritis since 1957 [27].

Disadvantages: Slow onset of therapeutic effect and significant ocular toxicity seemed to have shadowed the clinical supremacy of these drugs.

Uricosiric Agents

Such drugs that help in the enhanced excretion of excess uric acid through urination and thus reduce the urea concentration in the plasma are known as uricosiric agents [28-33]. There are 2 important agents which are frequently used in hyperuricemia viz., sulfinpurazone and probenecid both of which enhance the level of pencilllin in plasma by inhibiting its secretion. Eg: Probenecid (Figure 5).



p-(dipropyl-sulfamoyl)benzoic acid

Figure 5: Probenecid.

Salicylic acid analogues

A good number of salicylic acid analogues have also been found to possess anti-inflammatory actions, e.g., aspirin, salol, salsalate, sodium salicylate, salicylamide, benorilate, choline salicylate, flufenisal etc., in addition to their antipyretic analgesic property [34-36]. Among them Aspirin is the most commonly used over the counter drug (Figure 6).

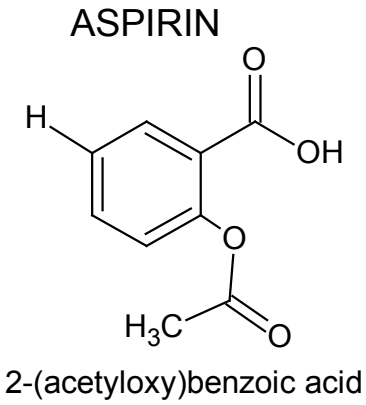


Figure 6: Aspirin.

GOLD COMPOUNDS

As the name denotes, drugs in this class are derived from the heavy metal gold (Au) [37]. They are the synthetic disease modifying antirheumatic drugs (DMARDs). Examples are: Auranofin, Aurothioglucose, Auruthioglucanide, sodium Aurothiomalate (Figure 7,8).

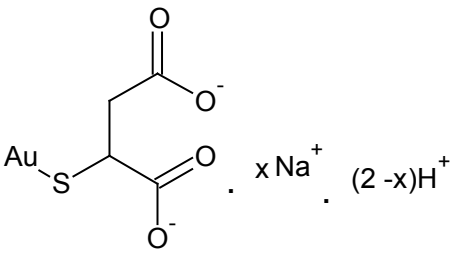


Figure 7: Sodium Aurothiomalate.

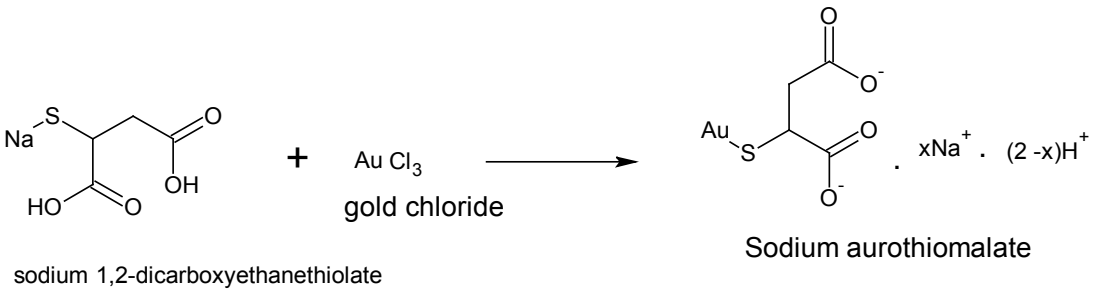


Figure 8: Synthesis of Sodium Aurothiomalate.

Structure activity relationship (SAR)

1. Compounds with the presence of aurous ion attached to ligand having sulfur possess pharmacological activity.

2. The gold compounds which are monovalent i.e., having aurous ion (Au^{+}) are more active than trivalent (auric ion, Au^{+3}) or colloidal gold compounds [38-40].

General adverse effects

1. Dermatological manisfestations like exfoliative dermatitis, vesicular dermatitis, erythema and popular dermatitis.
2. Heamatological disorders like thrombocytopenia, pururea, aplastic anaemia, eosinophilia and blood dyscrasias.

General therapeutic uses

1. Treatment of rheumatoid arthritis and progressive joint disease.
2. Treatment of atypical form of tuberculosis and bacterial endocarditis.

CONCLUSION

Non-steroidal anti-inflammatory drugs have been discussed briefly citing an example for each class. Gold compounds also have been discussed giving emphasis on its SAR; adverse effects; therapeutic effects as well synthesis of gold compounds. Use of gold compounds as inflammatory drugs has risen. Non-selective NSAIDs are indicated in the relief of all grades of pain and inflammation in a wide range of conditions, and are important treatments for arthritic conditions, acute musculo-skeletal disorders and other painful conditions resulting from trauma [41,42]. The adverse event profile of NSAIDs, including Cox-2 inhibitors, is known. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are class effects, although the exact incidence may vary between products. The CHMP noted that although the benefits of NSAIDs outweighed their risks, they should be used at the lowest effective dose and for the shortest possible treatment duration. All the chemical structures were drawn using software Chemdraw 8.0.

REFERENCES

1. Mizejewski GJ (2015) Alpha-Fetoprotein (AFP) and Inflammation: Is AFP an Acute and/or Chronic Phase Reactant? J HematolThrombo Dis 3: 191.
2. Ren W, Zhou H, Xian-Ju H, Gao Y (2014) Anti-Inflammatory Effects of Bullatine A on LPS-Induced RAW264.7 Cells by Endoplasmic Reticulum Stress. Interdiscip J Microinflammation 1: 123.
3. Sergio RC, Hernández L, Gallegos M (2015) Cannabinoids in Neuroinflammation, Oxidative Stress and NeuroExcitotoxicity. Pharm Anal Acta 6: 346
4. Liu D, Huang Z, Huang Y (2015) Clinical Analysis of Fractional Exhaled and Nasal Nitric Oxide in Allergic Rhinitis Children. J Allergy Ther 6: 204.
5. Majeed S, Ahmad MS, Sharma S (2015) Dual Role of Inflammation in Prognosis and Prevention of Tuberculosis. J Clin Cell Immunol 6: 298.
6. Kalil MA (2014) Modern Treatment of Rheumatoid Arthritis in Cows. J VeterinarSciTechnol 5: 202.
7. Nguyen D, Banerjee N, Abdelaziz D, Lewis JH (2014) Trainees' Attitudes and Preferences towards the Use of Over the Counter Analgesics in Patients with Chronic Liver Disease. AdvPharmacoepidemiol Drug Saf 3: 167.
8. Petrofsky JS, Laymon MS, Alshammari F, Khowailed IA (2014) Evidence Based use of Heat, Cold and NSAIDS for Plantar Fasciitis.Clin Res Foot Ankle 2: 140.
9. Nagao M, Sato Y, Yamauchi A (2014) Meta-Analysis of Interleukin Polymorphisms and NSAID Usage Indicates Correlations to the Risk of Developing Cancer. Int J Genomic Med 2: 113.
10. YiannakopoulouECh (2014) Pharmacovigilance and NSAIDs J Pharmacovigilance 2: e116.
11. Nishimura N, Osawa H, Yano T, Shinhata H, Hayashi Y, et al.(2014) Prevention of Loxoprofen-Induced Small Intestinal Mucosal Injuries by Irsogladine Maleate. J Gastroint Dig Syst 3: 161.
12. Nalamachu S, Pergolizzi JV, RaffaRB,Taylor R (2013) Acute Pain Management in the Emergency Department: Emphasis on NSAIDs. Emergency Med 4: 171.

13. Sultana N, Arayne MS, Khan MM, Ali SN (2013) Development of Liquid Chromatography–UV Method for Simultaneous Determination of Leflunomide and NSAIDs in API and Pharmaceutical Formulations: It's Application to In vitro Interaction Studies. Med chem 3: 262-270.

14. Sultana N, Naveed S, Arayne MS (2013) Facile and Manifest Liquid Chromatographic Method for the Simultaneous Determination of Enalpril Maleate and NSAIDs in API and Pharmaceutical Formulations. Pharm Anal Acta S2: 004.

15. Naveed S, Sultana N, SaeedArayne M, Siddiqui R, Mehboob M(2013) In vivo Interaction Studies of ACE Inhibitors with NSAIDs on Carrageenan Induced Inflammation.Clinic PharmacolBiopharm 2: 108.

16. Sultana N, SaeedArayne M, Ali SN(2012) Ultra Sensitive Liquid Chromatographic Method for the Simultaneous Determination of Carbamazepine with Nsaids in API, Pharmaceutical Formulation and Human Serum by Programming the Detector: Application to In Vitro Drug Interaction. J Chromat Separation Techniq 3: 15.

17. Salim N, Basri M, Abd. Rahman MB, Abdullah DK, Basri H, et al. (2011) Phase Behaviour, Formation and Characterization of Palm-Based Esters Nanoemulsion Formulation containing Ibuprofen. J NanomedicNanotechnol 2: 11

18. Lemke TL, Williams DA, Roche VF, Zito SW (2008) Foye's principles of medicinal chemistry. 6thed. New Delhi: Wolters Kluwer/Lippincott Williams & Wilkins.

19. Block JH, Beale JM (2004) Wilson and Gisvold's text book of organic medicinal and pharmaceutical chemistry. 11th ed. Baltimore: Lippincott Williams & Wilkins.

20. Abraham DJ (Ed.) (2007) Burger's Medicinal chemistry and drug discovery. (6thedtn) Vol 1-6. New Jersy: John Wiley & Sons.

21. Finar IL (2006) Organic Chemistry-stereochemistry and the chemistry of natural products. (5thedtn) Vol 2. Delhi; Doring Kindersley (India) Pvt. Ltd.

22. Rang HP, Dale MM, Ritter JM, Moore PK (2003) Pharmacology. (5thedtn). Edinburgh: Churchill Livingstone.

23. Ilango K, Valentina (2007) Text book of Medicinal Chemistry. (1stedtn). Vol-2. Chennai: Keerthi publishers.

24. Loetscher P, Dewald B, Baggiolini M, Seitz M (1994) Monocyte chemoattractant protein 1 and interleukin 8 production by rheumatoid synoviocytes. Effects of anti-rheumatic drugs. Cytokine 6: 162–170

25. Edward Tiekink RT (2003) Gold compounds in medicine: Potential anti-tumouragents.Gold Bulletin 36: 117-124.

26. Brown DH, Smith WE (1980) The chemistry of the gold drugs used in the treatment of rheumatoid arthritis. Chemical Society Reviews 9: 217-240.

27. Finkelstein AE, Walz DT, Batista V, Mizraji V, Roisman V, Misher A (1976) Auranofin. New oral gold compound for treatment of rheumatoid arthritis. Ann Rheum Dis 135: 251-257

28. Simas TAM, Corvera S (2014) The Roles of Adipose Tissue and Inflammation in Gestational Diabetes Mellitus. Intern Med S6: S6-010.

29. Patsouris D, Jeschk MG (2014) Stress Induced Insulin Resistance in Regards to Cellular Organelles, Inflammasome and Inflammation and Lipids. MolBiol 3: e114.

30. Lewis M, Merched AJ (2014) Tumor-Associated Macrophages, Inflammation and Pathogenesis of Hepatocellular Carcinoma. J MolGenet Med 8: 132.

31. Altman R, Keenan AH, Newman JW, Rutledge JC (2014) The Postprandial Effects of a Moderately High-Fat Meal on Lipid Profiles and Vascular Inflammation in Alzheimer's Disease Patients: A Pilot Study. J Gen Practice 2: 186.

32. Bestawros M, Chidumayo T, Blevins M, Canipe A, Bala J, et al. (2015) Increased Systemic Inflammation is Associated with Cardiac and Vascular Dysfunction over the First 12 Weeks of Antiretroviral Therapy among Undernourished, HIV-Infected Adults in Southern Africa. J AIDS Clin Res 6: 431.

33. Gaba M, Mohan C (2015)Design, Synthesis and Biological Evaluation of Novel 1, 2, 5-Substituted Benzimidazole Derivatives as Gastroprotective Anti-inflammatory and Analgesic Agents

34. Badawi AH, Kiptoo P, Siahaan TJ (2014) Immune Tolerance Induction against Experimental Autoimmune Encephalomyelitis (EAE) Using A New PLP-B7AP Conjugate that Simultaneously Targets B7/CD28 Costimulatory Signal and TCR/MHC-II Signal.J MultScler 1: 131.

35. Lapidot M, Barash U, Zohar Y, Geffen Y, Naroditsky I, et al. (2015) Involvement of Heparanase in Empyema: Implication for Novel Therapeutic Approaches. J Clin Cell Immunol 6: 29

36. Cantani A (2014) Immunological Properties of Breast Milk: A Prospective Study in 589 Children. Interdiscip J Microinflammation 1: 127.

37. Heck TG, Ludwig MS, Montagner GFFDS, Frizzo MN (2015) Subclinical Processes in the Development of Type Two Diabetes. J Nov Physiother 5: 246.

38. Cantani A (2014) Role of DermatophagoidesPteronyssinus in the Skin Lesions of Atopic Dermatitis in Children. Interdiscip J Microinflammation 1: 126.

39. Jedlicková L, Merkovská L, Jacková L, Janicko M, Fedacko J, et al. (2014) Ivabradine Significantly Decreases hsCRP and Increases the Activity of Glutathione Peroxidase in Patients with Stable Coronary Artery Disease. Interdiscip J Microinflammation 1: 125.

40. Herbert C, Bunting MM, Lambie N, Thomas PS, Kumar RK (2015) Immunoreactivity for Interleukin-33 in Allergic Airway Inflammation J CytolHistol 6: 302.

41. Madhavan PN, Gloria F, Gianna C, Karla M and MariselaAgudelo(2015) Alcohol Versus Cannabinoids: A Review of Their Opposite Neuro-Immuno-modulatory Effects and Future Therapeutic Potentials. J Alcohol Drug Depend 3: 184.

42. Spasovski D and Sotirova T (2014) Link between Dimethyl arginine Derivats and Acpa Antibodies in Patients with Rheumatoid Arthritis. Interdiscip J Microinflammation 1: 122.