# ANTI BACTERIAL ACTIVITY OF NONSTEROIDAL ANTI INFLAMMATORY AGENTS AND THEIR DERIVATIVES

**Sajjad A. Hafedh[a], Sahar A. Hussein[b], Noor H. Naser[c]***

**Article History:** **Received**: 22.04.2022 **Revised**: 20.05.2022 **Accepted**: 02.06.2022

**Abstract**: The review show the role of Nonsteroidalanti inflammatory agents and their moieties in key biological processes. They are wide used group of medicines derivatives utilized to treat a variety of medical pain conditions. One of these classes of drugs is naproxen that is commonly utilized. Despite its gastrointestinal side effects, most of this group of medicines was safely utilized for decades due to their low cost. They have reverse activities to inflammation, also pharmacological activity of non-steroidal anti-inflammatory medicines, such as antibacterial properties, have been the subject of considerable research in recent years, NSAIDs medicines works in manner that inhibiting all enzymes of cyclooxygenase group. This mechanism is interested in the possibility that cyclooxygenase two enzyme inhibits microbial development, which is characterized by the appearance of cyclooxygenase two enzyme. NSAIDs having derivatives molecules, they were always explored.

**Keywords:** Anti-bacterial activity, Nonsteroidal, inflammatory agents

[a]. Pharmaceutical chemistry department, Faculty of pharmacy, Kufa University, Najaf, Iraq
[b]. Pharmaceutical chemistry department, Faculty of pharmacy, Kufa University, Najaf, Iraq.
[c]. Pharmaceutical chemistry department, Faculty of pharmacy, Kufa University, Najaf, Iraq.

***Corresponding Author**

**Email:**noorh.naser@uokufa.edu.iq,
**DOI:** 10.31838/ecb/2022.11.03.002

## INTRODUCTION

NSAIDs are the common estmedicines utilized in the all countries. They are commonly used at doses proved for many diseases. They are known to stop the cyclooxygenase groups of enzymes; the mechanism of inhibition is shown in figure (1) below.

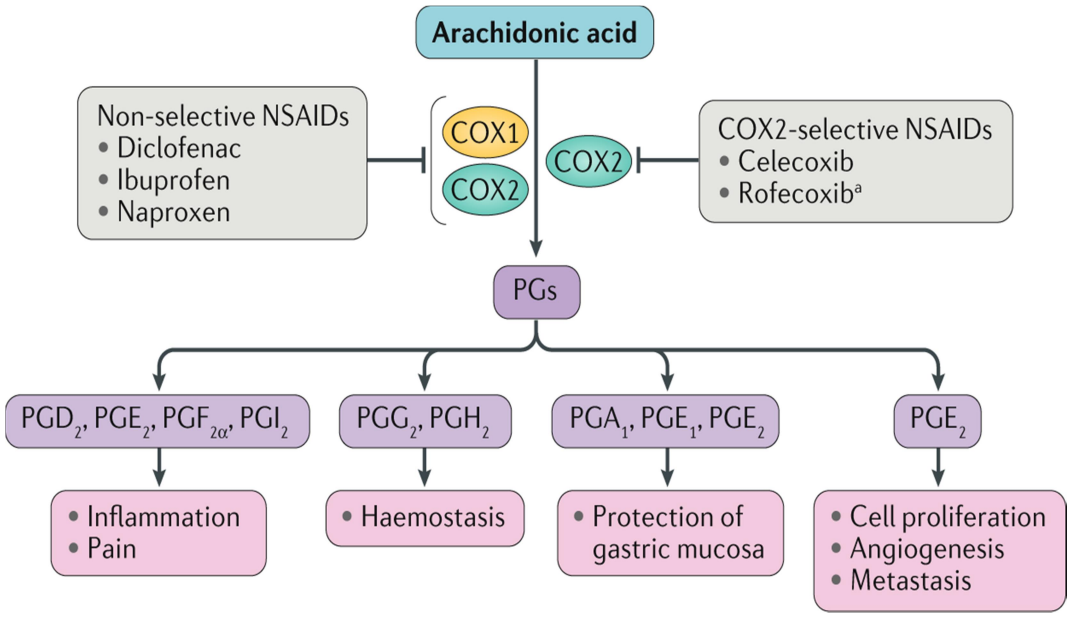
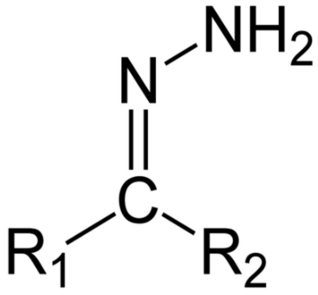



**Figure 1: The manner of inhibition by NSAIDs medicines**

Non-steroidal anti-inflammatory medicines have gastrointestinal upset. Several of these drugs have a accepted cardiac safety profile, on the other hand they could have gastrointestinal adverse effect. NSAIDs give an algesic, anti-inflammatory, and antipyretic actions. They are well known as a good medical group that stops both the enzyme of cyclooxygenase 1 and 2. Therefore, masking of the groups on the Non-steroidal anti-inflammatory medicines (active groups) may be a interested ways to lower the gastric and intestinal adverse effects. The etherification way to make prodrugs of non-steroidal anti-inflammatory medicines as new molecules were mentioned to elevate the

utilization of this groups of drugs in many therapeutic areas for utilizing NSAIDs by mouth delivery .Recently, number of kinds of bacteria have recognized to resist medicines as a sequence of the false utility of antibiotics, deficiency in the moieties and synthesis of moieties without strong action courage the researchers to develop new types of medicines that have anti bacterial actions. *Alijenab et al.* worked on more those six NSAIDs, from them naproxen towards twin types of skin fungal microbial types (dermatophyte). To stop growing of these fungi, diclofenac, aspirin, and naproxen approved to have high ability to do this actions. *Trichophyton mentagrophytes* showed more closed sensitivity to more tested compounds than Epidermophyton floccose. Many NSAIDs may have the ability to suppress harmful fungus; however, others may have potential efficacy against fungal growth. . Non-steroidal anti-inflammatory medicines were tested for their action against bacteria, in vitro against both the two gram Ve+ and VE- kinds of bacteria. The synthetic process and pharmacological testing of huge types of hydrazones (1) containing molecules have been taken as examples toward diverse pharmacological aims. Complexes of NSAIDs & Hydrazones have been showed to have anti-bacterial activities in vitro [1].



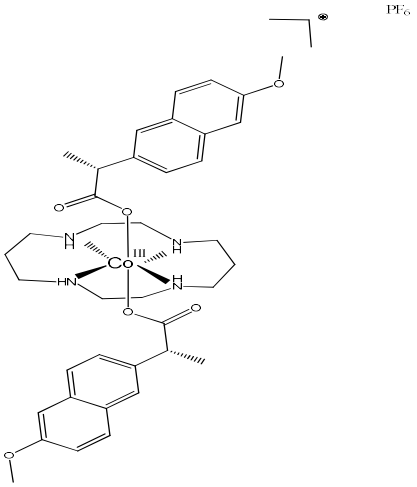

(1)

Furthermore, naproxen is considered to be a fruitful pioneer for novel influenza A virus antiviral compounds. The esters of NSAIDs have been synthesized with tocopherol, and gave accepted range from reverse action to oxidant, inflammation and other properties. NSAIDs are the commonest therapeutically class of drugs that used in researches for anticancer and antibacterial, and anti viral activities. Biological studies have shown that zinc complexes have antibacterial actions towards both gram-negative and gram-positive bacteria. They found a strong growth inhibition around disks of complexes against E. coli and Salmonella [2]. Hasan et al. (2015) discovered that a few non-steroidal anti-inflammatory drugs, such as naproxen metal complexes, had broad cytotoxic and antibacterial properties. Non-steroidal anti-inflammatory medications compound such naproxen silver and cobalt complexes revealed remarkable antibacterial action against a variety of pathogens. The complexes are monitored toward gram-positive bacteria *(Micrococcus luteus and S. aureus) and* gram-negative bacteria *(P. aeruginosa, Proteus mirabilis, E.coli, and Klebsiella pneumoniae)* in vitro using the agar well diffusion procedure to detect the impact of metal ions on anti-bacterial activity. They also discovered that the complexes had different actions toward different bacteria, and that the activity of the complexes differs from that of the parent ligands [3].

**Anti bacterial activity of Nonsteroidal anti inflammatory agents and Their Derivatives**

As a result of the overuse of antibiotics in recent years, several bacteria species have developed resistance. Researchers were prompted to produce new antimicrobial molecules due to a lack of novel medication molecules and the production of molecules with no substantial effects. The effects of seven nonsteroidal anti-inflammatory medications (NSAIDs), including naproxen, on two species of skin pathogenic fungus were studied by *Alijenab* (dermatophyte). The inhibition percent was reported in efficient agents. Three types of NSAIDs were substantially much effective at inhibiting the growth of dermatophyte. *Trichophyton mentagrophytes* showed more closed sensitivity to more tested compounds than Epidermophyton floccose. Many NSAIDs may inhibit harmful fungus, while others may have antifungal action. [4].*Mamatha et al*. used naproxen and 4-methylpentan-2-one to make the title chemical, which is a naproxen derivative (1,3-dimethyl-butylidene) hydrazine. They showed that this chemical had antibacterial activity towards both types of gram VE+ and gram VE- types in vitro. Vast number of hydrazone moeities was gain complete synthesis and pharmacologically tested for a variety of pharmacological purposes. In vitro, naproxen hydrazones showed anti-mycobacterial activity [5]. Without the donor ligands of nitrogen, Cihiniforoshan et al. made complexes of zinc (II) with naproxen once and ibuprofen once again. The binding mechanisms of donors in complexes are developed using molecular modeling of the complexes. Zinc complexes were seen to give antibacterial action against both gram ve- and gram ve+ bacteria in biological studies. They reported a considerable growth inhibition surrounding disks of complexes against *E. coli and Salmonella.*[6].The researchers created and analyzed numbers of new complexes of zinc-naproxen . Using the agar well diffusion method in laboratory, all complexes were tested against gram ve+ bacteria (*Micrococcusluteus and S. aureus*) and gram ve-types*(P. aeruginosa, Proteus mirabilis, E.coli, and Klebsiella pneumoniae*) to determine the effects of the metals on antibacterial actions. All of the complexes had different activity against different bacteria, and the activity of the complexes was compared to the activity of the parent ligands. Researchers used a quasi micro-assay with a previously self-developed quantified in vitro approach to study anti-malarial complexes. Researchers set out to create method called (transition metal complexes) and explore the effects of naproxen and its complexes on cytotoxicity, antibacterial activity. Copper, cobalt, iron, silver, and zinc complexes with naproxen as shown in complex 1.The disc diffusion method was used to assess antibacterial activity, as with cobalt and copper complexes, naproxen silver and zinc complexes showed substantial antibacterial action against certain of the pathogens studied. The iron complex of naproxen showed moderate antibacterial and cytotoxic action. Few complexes of naproxen with metals have extensive cell killing and antibacterial properties, according to this research. Naproxen silver and cobalt complexes (2) showed significant antibacterial action against a variety of microbes [7-8]. On refluxing naproxen, number of novel substituted compounds was created as a coupling reagent in the presence of distills and dries SiCL4. The cup plate method was used to test the antibacterial activity of the produced compounds towards *Staphylococcus aureus, Escherichia coli, P. aeruginosa, and Bacillus subtilis*. Four compounds outperformed the conventional antibiotic ciprofloxacin in antibacterial activity. Some of the naproxen amide prodrugs gave accepted antibacterial actions with the comparison to the pioneer medication [9].

(2)



According to *Neeraja et al*., Twenty thiazolyl and oxadiazole moieties, having the same properties of structure for the naproxen and ibuprofen, were derived by utilizing a copper-catalyzed azidealkyne cycle addition approach. When demonstrated towards three gram ve- and three gram ve+ bacteria, several from these compounds obtained good to moderate antibacterial activity [10].The activity of NSAIDs on test of bacterial resistance also the modification of bacterial pumping flow were investigated by researches. They looked and tested the activity of twelve NSAID active compounds, including naproxen, against eighty nine gram-negative rod strains and minimum inhibitory concentrations were calculated[11].*Eissa et al* derived and tested a novel series of (6-methoxy-2-naphthyl) propanamide derivatives for anti-bacterial actions. The MIC of these compounds was evaluated using a micro-dilution approach towards number of different bacteria types (3 Gram ve+ types (*B. subtilis, Streptococcus pneumonia, and S. aureus*) and twice for Gramve-types (*Salmonella typhimurium and E. coli*). According to the results of anti-bacterial actions, there are two of compounds have significant anti-bacterial activity against the *B. subtilis* [12]. By the reaction of Schiff –base, ligand generated from naproxen andC7H5BrO2, researchers synthesized, recognized and evaluate the anti-bacterial of transition of complexes of metals. They tested the ligands of Schiff base and its metal complexes towards several bacteria species to get their bioactivity profile shown in below figure (2). The complexes discovered have valuable antibacterial action. In comparison to the other species, the complexes were more effective against *Bacillus subtilis*.

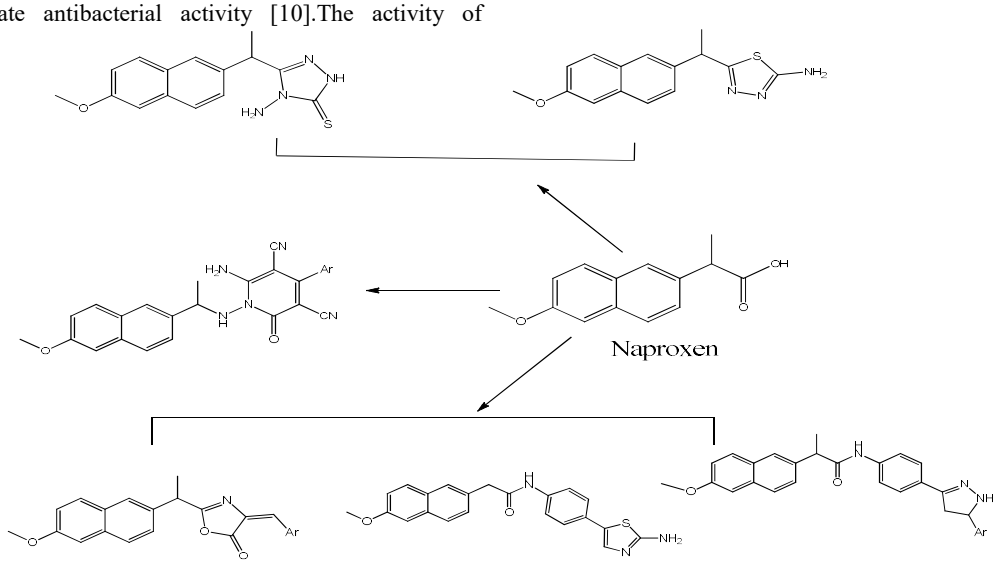
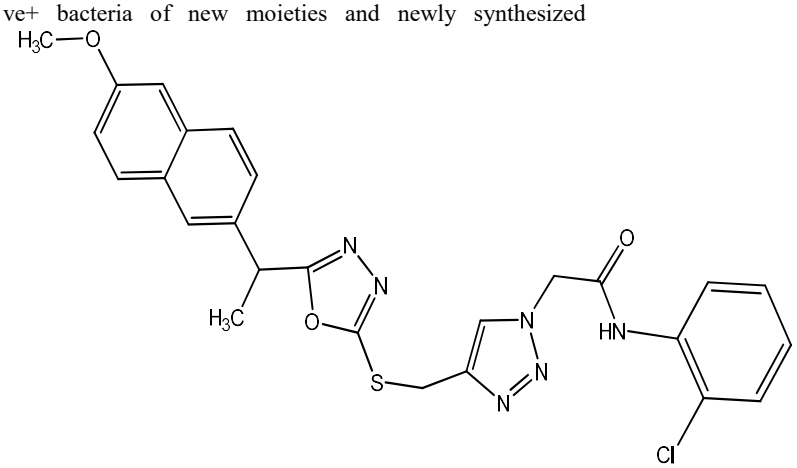



**Figure 2: ligand generated from naproxen and 5-bromosalicylaldehyde Schiff base reaction**

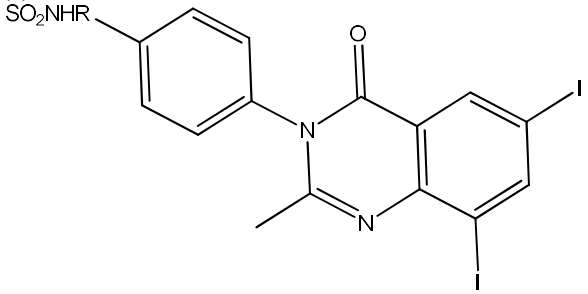
Several of compounds showed good to moderate anti-bacterial activity when tested against gram-ve- and gram ve+ bacteria of new moieties and newly synthesized chemical rings In both species of bacteria, (3) showed promising activity[10].



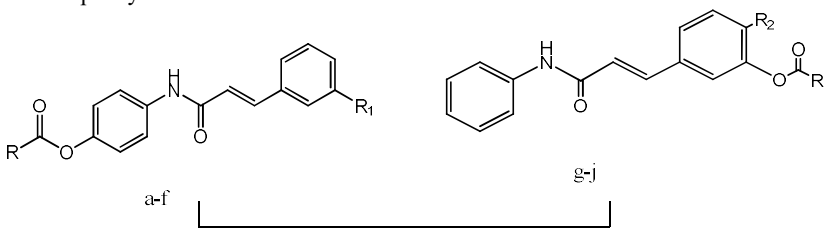
(3)

The activity against inflammation and bacteria of several novel synthesized derivatives rings were explored (4). All of the ingredients exhibited a significant antibacterial impact [13].

(4)




Synthesis, identifications, and anti-microbial evaluation of new chemical rings derivatives linked to aspirin and ibuprofen, with antibacterial activity assessed. Despite the parent chemicals' potential antibacterial activity (chalcones, aspirin, and ibuprofen), no synergism has been found.[14].In a laboratory test of Diclofenac sodium's in vitro antibacterial activity utilizing special technique , Diclofenac sodium was gave very good anti-microbial activities after 24 hours of incubation at 37 degrees Celsius .In vitro tests have also revealed that has antibacterial action against aggressive Salmonella typhimurium strains[15].Diclofenac sodium in known doses have been proven to have in vitro action towards many bacteria in other research. *Staphylococcus spp, Pseudomonas spp and Escherichia coli* were presented in the biofilms and treated with diclofenac sodium in known concentrations [16].Alem et al, 2004 showed that three NSAIDs were shown to have the strongest inhibitory effects, with aspirin producing up to 95% inhibition. On the other hand the Biofilm development was similarly decreased by Celecoxib, nimesulide, ibuprofen, and Meloxicam, albeit to a lower amount. The inhibition of prostaglandin synthesis has been proposed as the mechanism by which NSAIDs prevent biofilm development [17]. The capacity of these medications to suppress biofilm formation has also been investigated; furthermore, their capability to eliminate established the film needs more investigations. Capacity of NSAIDs drugs to influence the integrity of bacteria's cytoplasmic membrane may be connected to their antibacterial mode of action. Antibacterial activity of NSAIDs has previously been proven towards a huge spectrum of Gram-negative and Gram ve+ microorganisms [18].Cell permeability to propidium iodide, K+ release inside the cells, and changes in the Physico-chemical properties of the surface of the bacteria have all been showmen, implying cytoplasmic membrane injury. Also components of their method of activity could include DNA synthesis inhibition, DNA replication prevention, and bacterial membrane repair[19].Antibiotics like ciprofloxacin and tetracycline's and nonsteroidal anti-inflammatory medications (NSAIDs) are frequently administered jointly because they assist to relieve discomfort and fever associated with bacterial infections[20].Diclofenac has been shown to interfere with DNA synthesis in addition , it have ability to damage the membrane of Listeria monocytogenes. At the same time, several writers claimed that NSAIDs work by inhibiting DNA synthesis by binding to the DNA polymerase subunits, limiting DNA replication and repair or impairing membrane activity [21]. The majority of the research looked at the impact of NSAIDs on plank tonic cell adhesion in the early phases of biofilm development. The antibiofilm mechanism of action of NSAIDs is not completely studied; nevertheless, low number of researches have looked into the possibility for the way of activity of NSAIDs in the management of synthesized biofilms, emphasizing the necessity for further studies [23} Piroxicam, Meloxicam, and ketoprofen on the other hand, had a high ability to destroy produced bio films of all S. Aureus strains examined while, Piroxicam was the only medicine that couldn't break down premade C. albicans biofilms [22]




| Compound code | R | $R_1$ | $R_2$ |
|---|---|---|---|
| a | Aspirin | H | - |
| b | Aspirin | NO2 | - |
| c | Aspirin | Cl | - |
| d | Ibuprofen | H | - |
| e | Ibuprofen | NO2 | - |
| f | Ibuprofen | Cl | - |
| g | Aspirin | - | H |
| h | Aspirin | - | OCH3 |
| i | Ibuprofen | - | H |
| j | Ibuprofen | - | OCH3 |

**Figure 3: Novel n- phenylcinnamamide derivatives related aspirin and ibuprofen**

The copper (Asp) 2Cl2 complex has the strongest inhibitory impact against Bacillus subtilis, while Ni (Asp) 2Cl2 has the weakest. The Aspirin metal complexes have more action than the original aspirin at low concentrations[23,24].In 2020 researchers just proved an intriguing research examining the in laboratory efficacy of NSAIDs towards biofilms of *E. coli and S. aureus*. The tests revealed that three NSAIDs have anti-biofilm actions at doses comparable to those seen in human plasma concentrations of humans . Antibacterial and anti-biofilm activities of NSAIDs are thought to be mediated by a variety of mechanisms, which vary depending on the species.

NSAIDs, for example, appear to have antibacterial or anti-biofilm activity in S. aureus. P. aeruginosa is inhibited by ASA, and salicylate lowers extracellular polysaccharide synthesis [25]. Nearly, Non steroidal anti inflammatory agents may be used as an alternate treatment for a wound that is slow to heal or has clinical signs of a developed biofilm. Biofilm production may be connected to the presence of Staphylococcus spp. and Enterococcus spp. in periprothetic joint infections. Other causes of periprothetic joint infections include staphylococcal intracellular internalization, especially "Small colony variation" strains, as well as some strains may invade and colonize in the lacuna-canalicular system of cortical bone. A clinical trial looked at whether ASA could help patients with periprothetic joint infections keep their infections under control (PJIs) [26]. Ibuprofen and acetaminophen both inhibited bacterial growth in the same way. On isolated bacterium strains, they showed an antimicrobial impact. This in vitro activity must be further developed for in vivo testing, and more research is required to corroborate our findings. Ibuprofen has well-documented therapeutic effects in the treatment of long term (chronic) inflammatory cases in lung disease like( cystic fibrosis ), due to its capability to operate on high number of pathway to prevent inflammations. However, a few studies have found that ibuprofen has antimicrobial characteristics ranging from stopping bacterial growth to kill bacterial cells against a variety of infections, as well as synergy with other antimicrobials [27]. Number of NSAIDs was observed to exhibit antibacterial and synergistic actions, which have been detailed. These findings suggest that the reported positive benefits in Cystic fibrosis lung illness may be attributable to both activities against inflammation and bacteria rather than only the anti-inflammatory activity [28]. Researchers wanted to evaluate the direct antimicrobial effects of ibuprofen on two significant CF infections*: Pseudomonas aeruginosa and Burkholderia spp.*, because the direct anti-microbial actions of ibuprofen on Cystic fibrosis -associated Gram ve- pathogens had never been studied before. Furthermore, research used ibuprofen in g/mlat known concentration which are physiologically feasible and have previously been demonstrated to be effective in CF patients [29]. Using a high-throughput spot culture growth inhibition assay in vitro, Guzman et al. report full growth stopping of M. tuberculosis spp at a known concentration of ibuprofen.

## CONCLUSION AND PERSPECTIVES

Our research (review) concentrated on nonsteroidal anti-inflammatory drugs and their synthetic derivatives, with the goal of studying and developing new antibacterial medication candidates. NSAIDs have a wide range of biological actions and are a key component in the developing of biologically active moieties, the application of innovative synthesis methods and models to the synthesis of non-steroidal anti-inflammatory drug derivatives molecules. The struggle appears to have switched in favor of bacteria, as many bacteria have gained resistance to several antimicrobial treatments. Infectious diseases are now the world's largest cause of morbidity and mortality. Lower respiratory infection, diarrheal illnesses, HIV/AIDS, and malaria are among the top ten contributors to morbidity and mortality, according to a WHO assessment of these diseases [31]. Antibiotics and chemical compounds are commonly employed in the treatment of bacterial infections, but they have a number of drawbacks, including resistance, adverse effects, and high prices. Alternative antibacterial that are more effective, less resistant, and less harmful are needed. Recently, the possibility of a shortage of antimicrobials has become a significant issue.

**Ethical approval:** The research involves a computerized study and not involved any in vitro or in vivo experiments, so; not required approval from the ethical committee.

**Funding details:** N/A

**Conflict of interest:** N/A

**Informed Consent:** the study occurred on animals with the aid of computer software

**Authorship**
**Sajjad A. Hafedh:** Data analysis, draft writing
**Sahar A. Hussein:** Data, statistical analysis
**Noor H. Naser:** Main idea review draft writing, final approval

## REFERENCES

i. Dill, H, Hill, AGS. (1974). Naproxen. A new non-hormonal antiinflammatory agent. *Ann. Rheum. Dis*. 33, 12-19. http://dx.doi.org/10.1136/ard.33.1.12 PMID: 4595271.
ii. Lupulescu, A. (1996). Prostaglandins, their inhibitors and cancer. Prostaglandins Leukot. Essent. *Fatty Acids.* 54(2), 83-94.
iii. Angiolillo, DJ, Weisman, SM. (2017). Clinical Pharmacology and Cardiovascular Safety of Naproxen. *Am. J. Cardiovasc. Drugs*.
iv. Abdul Hussein, A, Al-Janabi, S. (2011). Investigation of antidermatophytic effects of non-steroidal anti-inflammatory drugs on Trichophyton mentagrophytes and Epidermophyton floccose. *J. Pharm. Res.* 10(3), 547-552. PMID: 24250387.
v. Mamatha, N, Babu, NS, Mukkanti, K, Pal, S. (201), 2-(6-methoxynaphthalen-2-yl) propionic acid (1,3-dimethyl-butylidene)-hydrazide. *Molbank*, 4, 1-4.
vi. Mahfouz NM, Omar FA, Aboul-Fadl T. (1999). Cyclic amide derivatives as potential prodrugs II: N-hydroxymethylsuccinimide-/isatin esters of some NSAIDs as prodrugs with an improved therapeutic index. *Eur J Med Chem.* 34(7-8): 551-562.
vii. Chiniforoshan, H, Tabrizi L, Hadizade, M, Sabzalian, MR, Chermahini, AN, Rezapour, M. (2014). Anti-inflammatory drugs interacting with Zn (II) metal ion based on thiocyanate and azide ligands: synthesis, spectroscopic studies, DFT calculations and antibacterial assays. *Spectrochim. Acta A Mol. Biomol. Spectrosc*. 128, 183-190.
viii. Abu Ali, H, Fares, H, Darawsheh, M, Rappocciolo, E, Akkawi, M, Jaber, S. (2015). Synthesis, characterization and biological activity of new mixed ligand complexes of Zn(II) naproxen with nitrogen based ligands. *Eur. J. Med. Chem.*, 89, 67-76. http://dx.doi.org/10.1016/j.ejmech.2014.10.032 PMID: 25462227.
ix. Neeraja, P, Srinivas, S, Mukkanti, K, Dubey, P.K, Pal, S. (2016). 1H1,2,3-Triazolyl-substituted 1,3,4-oxadiazole derivatives containing structural features of ibuprofen/naproxen: Their synthesis and antibacterial evaluation. *Bioorg. Med. Chem. Lett*. 26(21), 5212-5217.

x. Laudy, AE, Mrowka, A, Krajewska, J, Tyski, S. (2016). The influence of efflux pump inhibitors on the activity of non-antibiotic nsaids against gram-negative rods. *PLoS One*. 11(1), e0147131. http://dx.doi.org/10.1371/journal.pone.0147131 PMID: 26771525.

xi. Issa, SI, Farrag, AM, Shawer, TZ, Ammar, YA. (2017). Design, synthesis, 3D pharmacophore, QSAR, and docking studies of some new (6-methoxy-2-naphthyl) propanamide derivatives with expected anti-bacterial activity as FABI inhibitor. *Med. Chem. Res.* 26, 2375-2398.

xii. Shaheen MA, Feng, S, Anthony, M, Tahir, MN, Hassan, M, Seo, SY, Ahmad, S, Iqbal, M, et al. (2019). Metal-Based scaffolds of Schiff bases derived from naproxen: Synthesis, antibacterial activities, and molecular docking studies. *Molecules*. 24(7): 1237-1239. http://dx.doi.org/10.3390/molecules24071237 PMID: 30934936.

xiii. Alwash, AH, Mahdi, AMM, Al-Karagully, HA. (2018). *Asian Journal of Pharmaceutical and Clinical Research*

xiv. Dastidar, SG, Ganguly, K, Chaudhuri, K, Chakrabarty AN. (2000). The antibacterial action of diclofenac shown by inhibition of DNA synthesis. *Int. J. Antimicrob. Agents*. 14: 249-251.

xv. Lewis, K, (2001). Riddle of biofilm resistance. *Antimicrob. Agents Chemother*. 45: 999-1007.

xvi. Alem, MAS, Douglas, LJ. (2004). Effects of aspirin and other nonsteroidal anti- inflammatory drugs on biofilms and plank tonic cells of Candida albicans. *Antimicrob. Agents chemother*. 48: 41-47.

xvii. Abdul-Hussein, ZR, Zainab, R. (2014). Antibacterial Effect of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). *Antibacterial Effect of Non-Steroidal*.

xviii. Mohsen, A, Gomaa, A, Mohamed, F, Ragab, R, Eid, M, Ahmed, A.-H. Khalaf, A, Kamal, M, Mokhtar, S, Mohamed, H, et al. (2015). Antibacterial, anti-biofilm activity of some non-steroidal anti-inflammatory drugs and n-acetyl cysteine against some biofilm producing uropathogens. *Am. J. Epidemiol. Infect. Dis.* 3, 1-9.

xix. Jalil, H. A., Jasim, G. A., & Al-Sudani, B. T. (2022). The protective effect of small molecule SIRT1 activators on human corneal epithelial cells against oxidative stress. *Journal of Pharmaceutical Negative Results*, 13(1), 80-80.

xx. Mohsen, A, Gomaa, A, Mohamed, F, Ragab, R, Eid, M, Ahmed, A.-H, Khalaf, A, Kamal, M, Mokhtar, S, Mohamed, H, et al. (2015). Antibacterial, anti-biofilm activity of some non-steroidal anti-inflammatory drugs and n-acetyl cysteine against some biofilm producing uropathogens. *Am. J. Epidemiol. Infect. Dis.* 2015, 3, 1–9.

xxi. Ghali, H. G., & Abdulhamed, B. S. (2021). Treatment of Recurrent Minor Aphthous Stomatitis Using Diode Laser (940nm). *Journal of Population Therapeutics and Clinical Pharmacology*, 28(2).

xxii. Lawal, A, Obaleye, JA. (2006). Synthesis, characterization and antibacterial activity of aspirin and paracetamol- metal complexes. *BIOKEMISTRI.* 19(1):9-15

xxiii. Leão, C, Borges, A, Simões, M. (2020). NSAIDs as a drug repurposing strategy for biofilm control. *Antibiotics*. 9:591. doi: 10.3390/antibiotics9090591.

xxiv. Zoller, SD, Hegde, V, Burke, ZDC, Park, HY, Ishmael, CR, Blumstein, GW. (2020). Evading the host response: Staphylococcus “hiding” in cortical bone canalicular system causes increased bacterial burden. *Bone Res*.8:43.

xxv. Hersh EV, Hammond BF, Fleury AAP. (1991). Antimicrobial activity of flurbiprofen and ibuprofen in vitro against six common periodontal pathogens. *J Clin Dent*. 3:1–5.

xxvi. Zimmermann P, Curtis N. (2017). Antimicrobial effects of antipyretics. *Antimicrob Agents Chemother*. 61: e02268-16.

xxvii. Konstan MW, Byard PJ, Hoppel CL, Davis PB. (1995). Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med.* 332:848–854.

xxviii. Guzman JD, Evangelopoulos D, Gupta A, Birchall K, Mwaigwisya S, Saxty B, McHugh TD, Gibbons S, Malkinson J, Bhakta S. (2013). Antitubercular specific activity of ibuprofen and the other 2-arylpropanoic acids using the HT-SPOTi whole-cell phenotypic assay. *BMJ Open*. 3: e002672.

xxix. World Health Organization. (2014). *World Health Statistics 2014*.