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Review Article

The Role of Sulfa Drugs in our Life

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ABSTRACT

Gerhardt Dumac discovered in 1932 that Prontosyl kills bacteria while testing dyes, and in 1934, he began using Prontosyl as a treatment. This was in Germany, and experiments in France showed that the effect of Prontosyl is due to the presence of sulfanilamide in it. In 1908, Gelmo was the first to attend a sulfa drug conference in Germany. Sulfanilamide's medicinal usefulness was endorsed in 1936 by researchers at Johns Hopkins University in the United States, including Long and Plus, Marshall, and others. Sulfa drugs are used to treat a range of diseases caused by bacteria, with which it has been possible to save countless lives. It is believed that the effect of sulfa is to stop the growth of bacteria, meaning that these drugs prevent the growth and reproduction of bacteria, which creates an opportunity for the body's defensive forces to eliminate them. Humans are currently treated with sulfonamides for specific disorders, such as urinary system infections. However, sulfonamides are more typically seen in veterinary medicine. Therefore we attempted to explain the role and importance of sulfa drugs in our lives because of their widespread use in medical therapy.

Keywords: Sulfadrugs, Bacteria, Sulfanilamide, Cyclooxygenase, Human immunodeficiency virus.

INTRODUCTION

In recent years, modern antibiotic therapy has proven to be ineffective. In the early twentieth century, antibiotics were first utilised as growth enhancers in farm animals, which led to their introduction into the everyday human diet. As a result, a significant and hitherto unforeseen phenomenon emerged: the emergence of antibiotic resistance in bacteria (Dodds, 2017; Spisz *et al*., 2021). Antibiotic resistance causes 2.8 million illnesses in the United States every year. Sadly, more than 35,000 people die due to these illnesses (Control and Prevention, 2019; Spisz *et al*., 2021). Bacteria have evolved resistance to various antibiotics, including sulfonamides, over time (Spisz *et al*., 2021).

Discovery and use of Sulfa Compounds in the Treatment

Since the early twentieth century, sulphonamides have been used as medications when the discovery of sulphonamides and their derivatives for therapeutic purposes was a watershed moment in the history of chemotherapy. Gelmo *et al*. were the first to synthesise sulfonamides (Long and Wood, 1939; Hippensteel, 1986; Greenwood, 2008). In 1908, while conducting azo dye research. Hoerlien *et al*. found dyes containing the sulfanyl group that had an affinity for wool and silk proteins shortly after this study (Hörlein, 1936). Then in 1913, Eisenberg's found that chrysolite, a type of the azo dyes investigated, had a strong bactericidal effect in vitro. Until 1932 the medicinal benefits of sulfonamides were not determined. Prontosil((p-[2,4-diaminophenyl) azo]sulfanilamide) was shown to have significant antibacterial activity in vivo by German researchers. Then Domagk et al. discovered that prontosil could heal mice with streptococcal septicemia. Also, Domagk observed that prontosil was quickly converted to sulphanilamide, Fig. (1) in the cell and that the true antibiotic was the sulfanilamide, not the prontosil (Domagk, 1935; Trefouel, 1935; Vest *et al.*, 1938; Burkhard *et al.*, 1962; Combs, 1997; Wainwright and Kristiansen, 2011; Patrick, 2013; Ali *et al*., 2016).

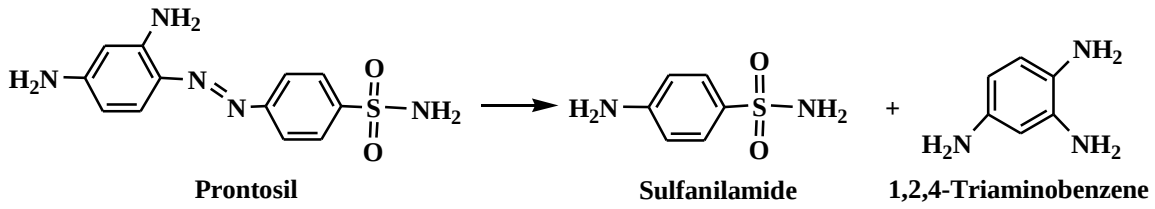

Fig. 1: Prontosil metabolism in vivo (Tačić *et al*., 2017).

Sulfonamides are an organic compounds with the general structure of Fig. (2). R might be alkyl, aryl, or hetero aryl in this structure (Baran *et al*., 2011; Ali *et al*., 2016).

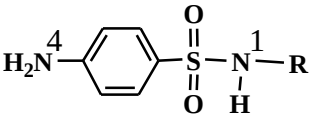

Fig. 2: Structure of sulfonamide (Tačić *et al*., 2017).

During the late 1930s, many different sulfonamides were developed. Many of them were significant against the activity of an antibacterial range of pneumococci and streptococci. In 1941, many sulfa pyrimidines were introduced (Combs, 1997). As a result of this advancement, a slew of new opportunities a Sulfonamides are being created. There are about 5,000 drugs already on the market, but only 33 have been approved for use in general medicine (Cates, 1986; Ali *et al*., 2016). It was the first study of synthesised organic compounds as potential medications to combat infection spread through the bloodstream (Hossain, 2005; Ali *et al*., 2016).

Sulfa Drugs used in the Treatment

Sulfa Drugs Act as an Antibacterial

The activity of sulfa medications has been widely investigated and can be summarised as follows. Bacteriostatic dosages of sulfonamides are used to prevent or limit bacterial proliferation. Sulfonamides hinder bacteria from producing folic acid, which has a bacteriostatic effect (Sánchez-Osuna *et al.*, 2019; Nunes *et al.*, 2020; Spisz *et al*., 2021). Bacteria produce folic acid on their own, by using endogenous chemicals and enzymes. Endogenous chemicals occur in the biological system naturally (Bayly and Macreadie, 2002; Iliades *et al*,, 2003). In particular, sulfonamides inhibit dihydropteroate synthetase, which converts of para-aminobenzoic acid (PABA) and dihydropteroate diphosphate to dihydropteroate acid, which is considered a precursor to the synthesis of deoxyribonucleic acid (DNA) and folic acid. Sulfonamide competes with PABA on the "active site" of dihydropteroate synthase, producing them "competitive inhibitors" (Smith and Powell, 2000; Iliades *et al.*, 2003; Carter *et al*., 2007; Greenand and Matthews, 2007; Bhattacharjee, 2016; Jabbir, 2016).

Sulfonamides' structural similarity to para-aminobenzoic acid. Therefore, it "tricks" the enzyme into binding with sulfonamide rather than the endogenous molecule PABA. In the synthesis of folic acid, the replacement of the para-aminobenzoic acid by the sulfonamide results in the production of a "false" pathway Fig. (3), which cannot progress through the synthetic sequence (Valderas *et al*., 2008; Ali *et al*., 2016; Tačić *et al*., 2017; Dheyaa *et al*., 2022).

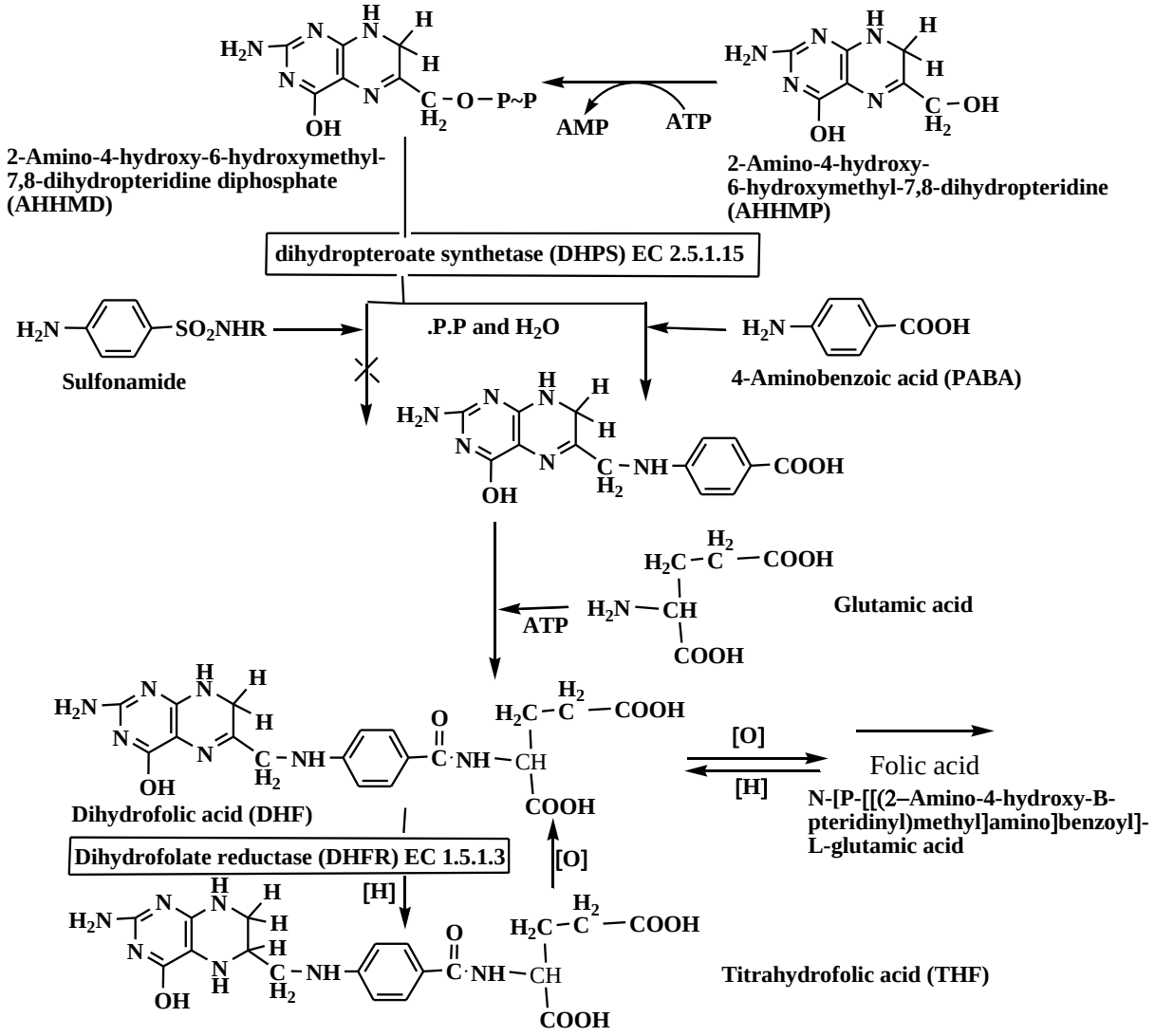

Fig. 3: Sulfonamide action mechanism (Ali *et al*., 2016).

Sulfonamides Inhibit the Activity of Carbonic Anhydrase

Carbonic anhydrase (CA) is an enzyme found in kidneys and erythrocytes (red blood cells). It catalyses the hydrating of CO_2 and the dehydration of bicarbonate at physiological pH ($CO_2+H_2O \rightarrow HCO_3$ -+H+), which is also known to be inhibited by sulfonamides (Ali *et al*., 2016; Supuran, 2016; Elgemeie *et al.*, 2019). The carboxylation stage of major metabolic processes such as ureagenesis, gluconeogenesis, lipogenesis, and the manufacture of pyrimidines and amino acids requires the creation of bicarbonate. Carbonic anhydrase regulates CO2 release from the body by transferring it from the tissue to the lungs. Due to its ubiquitous nature, it has been the target of inhibitors in the medical management of various illnesses. It's also in charge of electrolyte release in tissues and organs and maintaining homeostasis. Sulfonamides have been used to treat infections such as heart disease, glaucoma, epilepsy, nowadays and cancer for more than 50 years when it was discovered that they inhibit CA Since the 1950s, four sulfonamides have been used in clinical trials as systemic CA inhibitors: acetazolamide, methazolamide, ethoxzolamide, and dichlorphenamide Fig. (4). Dorzolamide and brinzolamide have been accessible as antiglaucoma prescription medications since the 1990s Fig. (4) (Ali *et al*., 2016; Scozzafava *et al.*, 2000; Supuran *et al.*, 2001; Vullo *et al*., 2003).

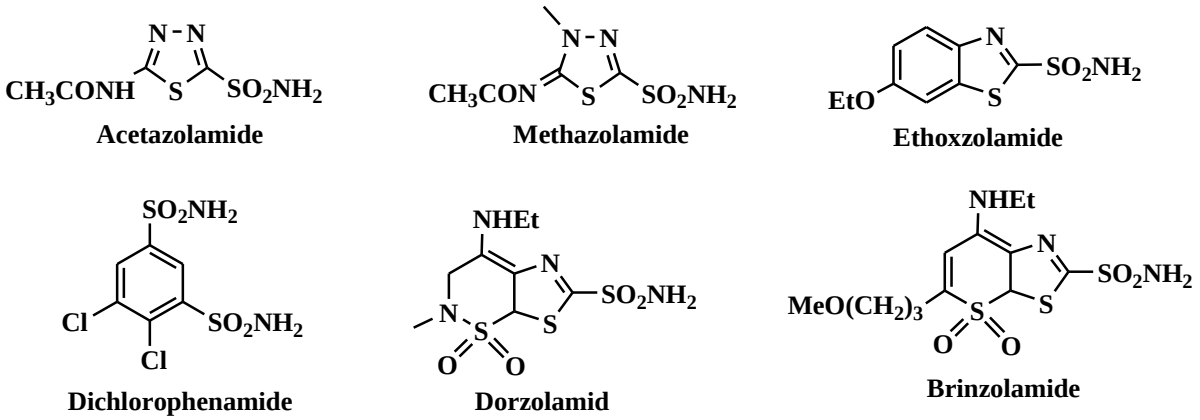

Fig. 4: Use some essential sulfonamides as a carbonic anhydrase inhibitor (Ali *et al*., 2016)

Sulfonamides Inhibit the Activity of Cyclooxygenase (COX):

Sulfonamides have been widely used as specific cyclooxygenase-II inhibitors since 1999. cyclooxygenase converts arachidonic acid to prostaglandins, which are responsible for various biological processes, including normal kidney function, platelet aggregation and hypertension, but most significantly, pain perception (Maier *et al*., 2004; Talley *et al*., 2000; Ali *et al*., 2016; Alaa *et al*., 2019). Cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) are the two subtypes of cyclooxygenase, with COX-II being the most important in provoked inflammatory reactions. As a result, since its discovery in 1991, COX-II has been a target for inhibition to decrease pain produced by osteoarthritis and rheumatoid arthritis. As a result, in 2002, the aryl sulfonamides celecoxib and valdecoxib in were identified as COX-II inhibitors Fig. (5) (Talley *et al.*, 2000; Chandna *et al.*, 2013; Ali *et al*., 2016).

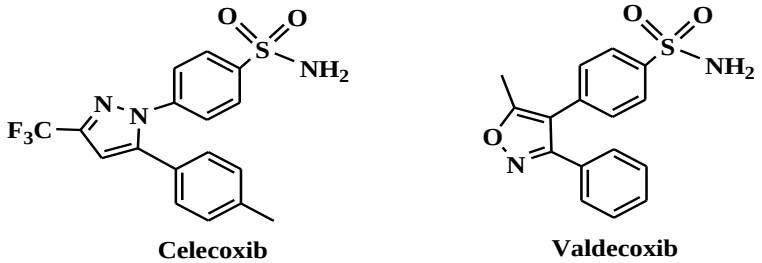

Fig. 5: Use of some essential sulfonamides as COX inhibitors.

Sulfonamides Activate Anti-Cancer Agents:

One of the sulfanilamide derivatives is chloroquinoxaline. Clinical trials are still ongoing Fig. (6). Chloroquinoxaline prevents the development of solid tumours in the breast, ovary, skin and lungs. While the exact mechanism of action is unknown. The effect of sulfonamides is noticeable. On the other hand, the lack of success is frustrating. During clinical trials for non-small cell lung cancer, this was implied. The development of a candidate clinical drug has been suspended. In 1992, Yoshino *et al*. reported that sulfonamide has low activity in vitro activity in tumour-bearing animals this promising result prompted the development of sulfonamide derivatives to develop better anti-tumour properties. As a result, Yoshino *et al*. whereas E7010 sulfonamide were identified as E7010 sulfonamide was proportional to the rate of tumour progression Fig. (6) E7010 has been clinically tested in phase I and II studies and is effective. Research is currently underway on a potential anti-tumour therapy (Yoshimatsu *et al.*, 1997), based on the structure of E7010, developed the second-generation sulfonamide ER-34410 Fig. (6). Less toxicity than E7010 could treat human tumour cell lines in vitro (Scozzafava *et al*., 2002; Ali *et al*., 2016). According to Ozawa *et al*. (2001) E7070 is the most effective anti-tumor sulfonamide yet Fig. (6) E7070 inhibited colon cancer cell growth in vitro and in vivo, and it can also cure lung and colon cancer (Ozawa *et al*., 2001; Ali *et al*., 2016). Anti-cancer drug E7070 (indisulam) is now in phase II studies (Dittrich *et al*., 2007; Ali *et al.*, 2016).

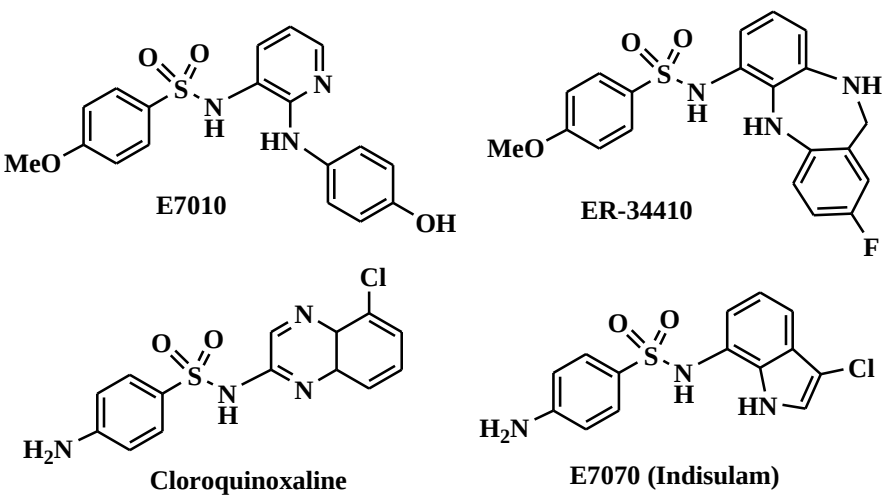

Fig. 6: Some important sulfonamides are used as anti-cancer agents. (Ali *et al*., 2016).

Sulfonamides Inhibitors a Human Immunodeficiency Virus (HIV):

Anti-human immunodeficiency virus (Anti- HIV) protease action is also a property of sulfonamides. The HIV protease is a homodimer with two aspartyl active sites (Asp25 and Asp125) that may cleave tough bonds like Tyr-Pro Phe-Pro, to name a couple of things. Several HIV protease inhibitors have been approved for use in clinical trials, they're readily available and frequently employed in tandem with reverse transcriptase., inhibitors to deliver the Highly Active Therapy, a multi-drug treatment. Antiretroviral Therapy is a type of antiviral medication used (HAART). Nonpeptidic amino acids are beneficial. Protease inhibitors have a higher bioavailability and a longer time to take effect, the rate of excretion of inhibitors is higher than that of peptide-based protease, one of them is protease inhibitors. Antiretroviral medicines Tipranavir and Amprenavir are two of them. Sulfonamide-based medicines Fig. (7) (Schobert *et al.*, 2008; Ali *et al*., 2016).

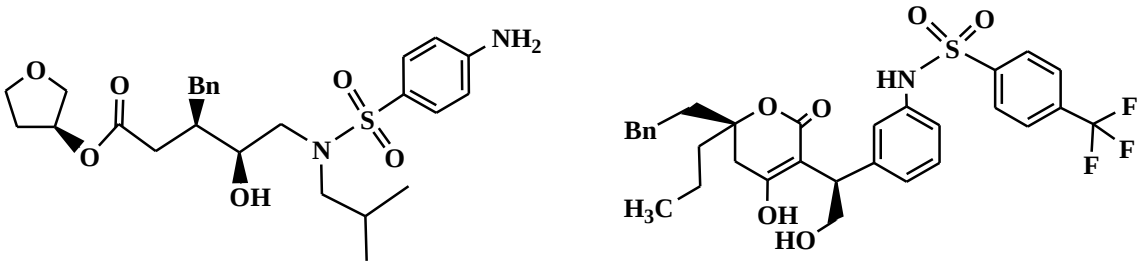

Fig. 7: Some important sulfonamides are used as anti-cancer agents (Ali *et al*., 2016).

Sulfonamide compounds treat several diseases

Several more sulfonamides have received clinical approval and are now used to treat various illnesses Fig. (8) sulfonamides like furosemide and torsemide are diuretics that help people with persistent systolic heart failure reduce their blood pressure. (Gottlieb *et al*., 1998; Jabbir, 2016). Glibenclamide is a sulfonamide used to treat diabetes mellitus type two (DMT2). Moreover, sildenafil is one of the most commonly used sulfonamide medications nowadays. Erectile dysfunction is treated with the drug sildenafil (Viagra) Fig. (8) (Ali *et al*., 2016).

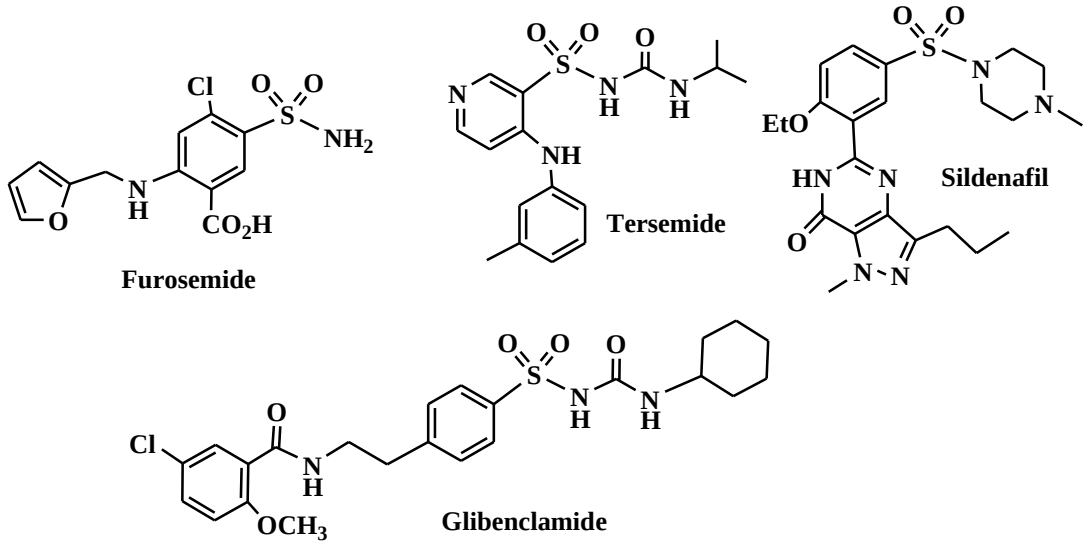

Fig. 8: Sulfonamide compounds treat several diseases (Ali *et al*., 2016).

The diseases that are affected by Bacteria:

The pathophysiology of bacterial infection includes the mechanisms that lead the development of illness signs and symptoms. Pathogenic bacteria can transmit, adhere to, and invade host cells and tissues. Toxicity and immunity evasion, many infections caused by pathogenic microorganisms are asymptomatic or undetected, microorganisms or immunological reactions to their appearance cause enough disease to cause disease (Ali *et al*., 2016), such as:

Pseudomonasaeruginosa:

Pseudomonas aeruginosa (P. aruginosa) is a Gram negative rod, an aeruginous has been linked to septicemia, urinary tract infection, corneal ulceration, endocarditis, and pneumonia (from ventilator and endotracheal tube) (Ali *et al.*, 2016).

Staphylococcus genus:

Staphylococcus is a genus of Gram-positive bacteria. Anterior skin, nares and mucous membranes proliferate asymptomatically. Around 20-30% of the populace is persistently colonised, with 30% temporary carriers (Wertheim *et al*., 2005). This bacterium has become the most

investigated staphylococcal species because of the abundance of antibiotic-resistant strains and the relevance of S.aureus infections (Kohanski *et al.*, 2010; Pospíšilová *et al*., 2018). Fig. (9) shows the overall mechanism.

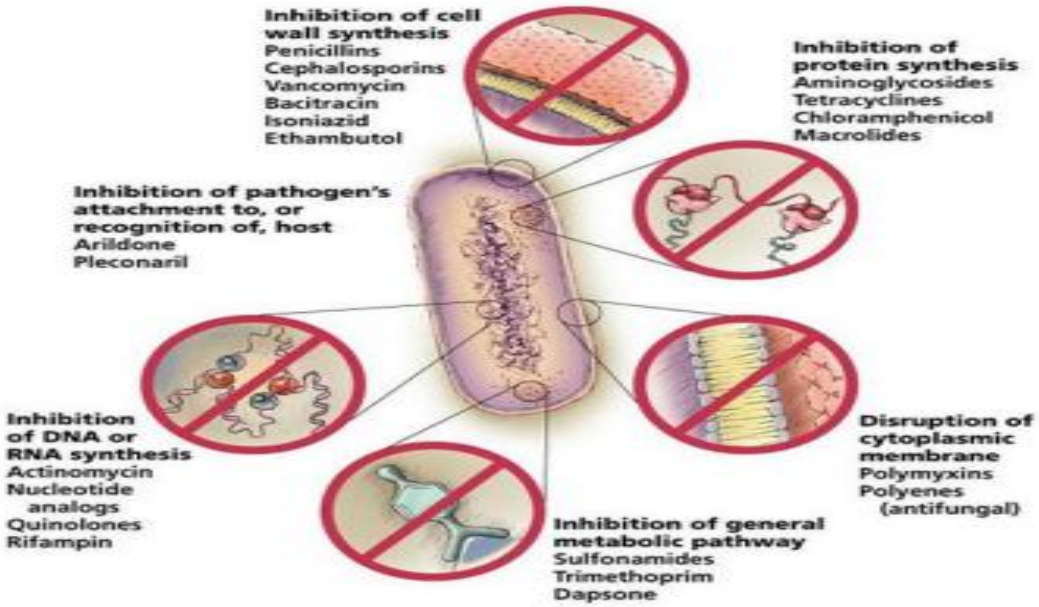

Fig. 9: Mechanism of antimicrobial action (Kohanski *et al*., 2010)

The role of antibiotics in inhibition of proteins synthesis for bacteria:

Many drugs such as tetracycline, chloramphenicol, aminoglycosides, lincomycin, and erythromycin have decreased the synthesis of proteins in bacteria. Antimicrobial medicines can inhibit protein synthesis in bacterial ribosomes by inhibiting transcription and translation of genetic material without having a significant effect on mammalian ribosomes because the chemical composition and functional specifications of each type of ribosome subunit differ sufficiently Fig. (10) (Mukhtar and Wright, 2005; Jabbir, 2016).

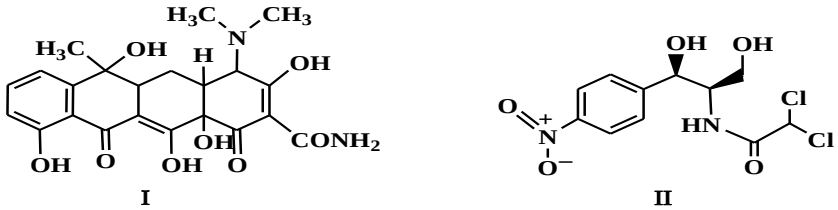

Fig. 10: Structures of Tetracycline (I) and Chloramphenicol (II)

The Role of antibiotics in inhibition of synthesis of Nucleic Acid :

A nucleic acid inhibitor is an antibacterial agent that inhibits the formation of nucleic acids. Inhibitors are classified into DNA and RNA inhibitors (Fletcher, 1984; Rubin *et al.*, 1986).

Sulfa medication side effects include:

Sulfonamide therapy may result in agranulocytosis, aplastic anaemia, hypersensitivity, acute hemolytic anaemia, gastrointestinal such as headache, anorexia, nausea, dizziness, mental depression, vomiting, and indications of central nervous system involvement. Hepatitis, a rare but potentially severe side effect of sulfonamide therapy, can occur (Hossain, 2005; Ali *et al*., 2016).

CONCLUSION

Sulfa drugs are used to treat a range of diseases caused by bacteria, with which it has been possible to save countless lives. It is believed that the effect of sulfa is to stop the growth of bacteria, meaning that these drugs prevent the growth and reproduction of bacteria, which creates an

opportunity for the body's defensive forces to eliminate them. Sulfa drugs may cause poisoning, so they should only be given under the supervision of a doctor. As a result of the emergence of resistant strains of the drug, its effect has become less. Antibiotics have largely replaced sulfa compounds in the treatment of bacterial infections.

Ethical Requirements Observation

There are no conflicts of interest declared by the authors.

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دور عقاقير السلفا في حياتنا

الملخص

اكتشف جيرهاردت دوماك في عام 1932 أن البرونتوزيل يقتل البكتيريا أثناء اختبار الأصباغ، وفي عام 1934 بدأ في استخدام البرونتوزيل كعلاج. كان هذا في ألمانيا، وأظهرت التجارب في فرنسا أن تأثير البرونتوزيل يرجع إلى وجود السلفانيلاميد فيه. في عام 1908، كان جيلمو أول من حضر مؤتمر سلفا للمخدرات في ألمانيا. تم اعتماد الفائدة الطبية للسولفانيلاميد في عام 1936 من قبل الباحثين في جامعة جونز هوبكنز في الولايات المتحدة، بما في ذلك Long and Plus و Marshall وغيرهم. تستخدم عقاقير السلفا في علاج مجموعة من الأمراض التي تسببها البكتيريا، والتي من خلالها كان من الممكن إنقاذ أرواح لا حصر لها. يُعتقد أن تأثير السلفا هو وقف نمو البكتيريا، مما يعني أن هذه الأدوية تمنع نمو البكتيريا وتكاثرها، مما يخلق فرصة لقوى الجسم الدفاعية للقضاء عليها. يعالج البشر حاليًا بالسلفونواميدات لعلاج اضطرابات معينة، مثل التهابات الجهاز البولي. ومع ذلك، تُرى السلفونواميدات بشكل أكثر شيوعًا في الطب البيطري. لذلك حاولنا أن نظهر دور وأهمية عقاقير السلفا في حياتنا بسبب استخدامها على نطاق واسع في العلاج الطبي.

الكلمات الدالة: عقاقير السلفا، البكتيريا، سلفانيلاميد، انزيمات الأكسدة الحلقية، فيروس نقص المناعة البشرية.