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Review Article

RECENT ADVANCEMENT OF CHALCONE DERIVATIVES AS ANTICONVULSANT,ANTI-INFLAMMATORY, ANT-MICROBIALACTIVITY: AN OVERVIEW

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Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids.Worldwide, approximately 40-50 million people suffer from epilepsy, a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior perception and/or consciousness. When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. by site of origin, aetiology, electro physiologic correlation, and clinical presentation It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized. The first effective AED was potassium bromide, discovered serendipitously in the mid nineteenth century. Phenobarbital came into use in the early twentieth century, followed by phenytoin in the late 1930s, the latter resulting from systematic investigations by Merritt and Putnam using an animal seizure model. A seizure is the clinical manifestation of a hyper excitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered— excitation predominates over inhibition. It mainly includes drug absorption, distribution, metabolism and elimination/ excretion. Drug interactions based on pharmacokinetics, or "what the body does to the drug," must be distinguished from those based on Pharmacodynamic, or "what the drug does to the body." Inflammation is a protective immunovascular response that involves immune cells, blood vessels, and molecular mediators Microorganisms are very diverse; they include bacteria, fungi, archaea, and protists; microscopic plants (green algae) and animals such as plankton the planarian and the amoeba.Fungi are heterotropic organism, they don't form embryos. Fungi are eukaryotic chemoorganiotropic organism that has no chlorophyll.

Keywords: Chalcone, AED, Seizures, antiseizure, Trimethodione, NSAIDs, Anti-microbial

INTRODUCTION

Worldwide, approximately 40-50 million people suffer from epilepsy, a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior perception and/or consciousness .Every year approximately 250000 new cases are added to this figure. Epilepsy is a brain disorder in which a person has repeated seizures (convulsions) over time. Epilepsy occurs when permanent changes in brain tissue cause the brain to be too excitable or jumpy. The brain sends out abnormal signals. This result in repeated, unpredictable seizures.[2] Symptoms vary from person to person. Some people may have simple staring spells, while others have violent shaking and loss of alertness [1-3].

Causes of Convulsion:

The causes of epilepsy can be divided into two groups' brain injuries and chemical imbalances in the brain. The type of injury that can lead to a seizure is age-dependent. Seizures in children often are caused by birth traumas, infections, such as meningitis, congenital abnormalities or high fevers. Seizures in the middle years commonly are caused by head injuries, infections, alcohol, stimulant drugs or medication side effects. In the elderly, brain tumours and strokes cause a higher proportion of seizures.[4]

Seizures can result from exposure to lead, carbon monoxide, and many other poisons. They also can result from exposure to street drugs and from overdoses of anti-depressants and other medications. Seizures are often triggered by factors such as lack of sleep, alcohol consumption, stress, or hormonal changes associated with the menstrual cycle. Smoking cigarettes also can trigger seizures. The nicotine in cigarettes acts on receptors for the excitatory neurotransmitter acetylcholine in the brain, which increases neuronal firing. Kidney failure or liver failure can also produce seizures. Genetics or heredity is most relevant to generalized seizures, including absence, generalized tonic-clonic and myoclonic seizures. Defects in genes don't directly lead to epilepsy, but they can alter the excitability of brain in a way to predispose to the seizures. Typically, epilepsy develops because of multiple gene abnormalities or because of a gene abnormality in concert with an environmental trigger [4-6]. Anything that disturbs the normal pattern of neuron activity from illness to brain damage to abnormal brain development can lead to seizures. Epilepsy may develop because of an abnormality in brain wiring, an imbalance of nerve signalling chemicals called neurotransmitters, or some combination of these factors. Neurotransmitters that decrease neuronal activity in the brain and either situation can result in too much neuronal activity and cause epilepsy. Neurotransmitter that plays a role in epilepsy is GABA, or gamma-amino butyric acid, which is an inhibitory neurotransmitter. Abnormalities in brain wiring that occur during brain development also may disturb neuronal activity and lead to epilepsy. The cell membrane that surrounds each neuron plays an important role in epilepsy. Cell membranes are crucial for a neuron to generate electrical impulses. A disruption in any of these processes may lead to epilepsy. In some cases, epilepsy may result from changes in non-neuronal brain cells. These cells regulate concentrations of chemicals in the brain that can affect neuronal signalling [7].

Idiopathic and Symptomatic Seizures:

In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in any of a variety of environmental factors, including alteration in blood gases, pH, electrolytes, blood glucose level, sleep deprivation, alcohol intake,

and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the primary focus. However, advances in technology have improved ability to detect abnormalities, and in some patients, neuroimaging techniques, such as magnetic resonance imaging (MRI), positron-emission tomography (PET) scans and single-photon-emission coherence tomography (SPECT) can identify areas of concern[8]. Epilepsy can be labelled idiopathic or symptomatic depending if the etiology is unknown, or is secondary to an identifiable.

Idiopathic epilepsy: When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. These seizures may result from an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiseizure drugs or vagal nerve stimulation. Most cases of epilepsy are idiopathic [9].

Symptomatic epilepsy: A number of causes, such as illicit drug use, tumours, head injury, hypoglycaemia, meningeal infection, or rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. When two or more seizures occur, then the patient may be diagnosed with symptomatic (secondary) epilepsy. Chronic treatment with antiseizure medications, vagal nerve stimulation and surgery are all appropriate treatments and may be used alone or in combination. In some cases when the cause of a single seizure can be determined and corrected, therapy may not necessary. For example, a seizure that is caused by transient hypotension or is due to a drug reaction does not require chronic prophylactic therapy. In other situations, antiseizure drugs may be given until the primary cause of the seizures can be corrected.[7, 10].

Classification of Seizures:

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, aetiology, electro physiologic correlation, and clinical presentation. Seizures have been classified into two broad groups: partial (or focal), and generalized.

Partial

Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Consciousness is usually preserved. Partial seizures may progress, becoming generalized tonic-clonic seizures.

Simple partial: These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity, which are confined to a single locus in the brain. The electrical discharge does

not spread, and the patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.

Complex partial: These seizures exhibit complex sensory hallucinations, mental distortion, and loss of consciousness. Motor dysfunction may involve chewing movements, diarrhoea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread and become complex and then spread to a secondarily generalized convulsion. Partial seizures may occur at any age.

Generalized

Generalized seizures may begin locally, producing abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness

Tonic-clonic: Seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

Absence: These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. This seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram [11].

Myoclonic: These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

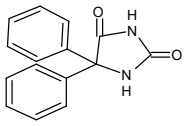
Febrile seizures: Young children may develop seizures with illness accompanied by high fever. This may occur in siblings. The febrile seizures consist of generalized tonic-clonic convulsions of short duration and do not necessarily lead to a diagnosis of epilepsy.

Status epilepticus: In status epilepticus, two or more seizures recur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment [12].

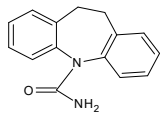
Anticonvulsant Drugs

The first effective AED was potassium bromide, discovered serendipitously in the mid nineteenth century. Phenobarbital came into use in the early twentieth century, followed by phenytoin in the late 1930s, the latter resulting from systematic investigations by Merritt and Putnam using an

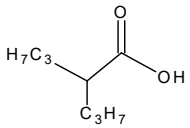
animal seizure model. Trimethodione, discovered in 1944, was the first AED specific for the treatment of absence seizures. The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers, and in the treatment of neuropathic pain. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, an effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. Some studies have cited that anticonvulsants themselves are linked to lower IQ in children. However these adverse effects must be balanced against the significant risk epileptiform seizures pose to children and the distinct possibility of death and devastating neurological sequela secondary to seizures. Anticonvulsants are more accurately called antiepileptic drugs (abbreviated "AEDs") or antiseizure drugs. Convulsive nonepileptic seizures are quite common and these types of seizures will not have any response to an antiepileptic drug. In epilepsy an area of the cortex is typically hyperirritable that can often be confirmed by completing an EEG. Antiepileptic drugs function to help reduce this area of irritability and thus prevent epileptiform seizures. Drug or vagal nerve stimulator therapy is the most widely effective mode for the treatment of patients with epilepsy. It is expected that seizures can be controlled completely in approximately 70 to 80 percent of patients with one medication. It is estimated that approximately 10 to 15 percent of patients will require more than one drug and perhaps 10 percent may not achieve complete seizure control [13]. Antiepileptic drugs (AEDs) are those which decrease the frequency and/or severity of seizures in people with epilepsy. The therapeutic goal is maximizing seizure control while minimizing adverse drug effects, thus improving the life.Older agents as exemplified by phenytoin, carbamazepine, valproate, the benzodiazepines, ethosuximide, Phenobarbital, primidone, and trimethadione. Newer agents consisting of vigabatrin, gabapentin, felbamate, amotrigine, carbazepine, zonisamide, tiagabine, topiramate, and levetiracetam [14].



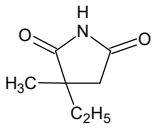
Phenytoin



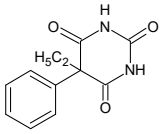
Carbamazepine



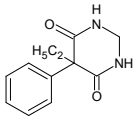
Valproic acid



Ethosuximide



Phenobarbital



Primidone

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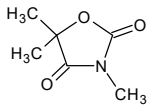
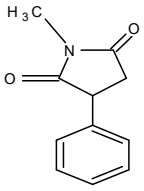
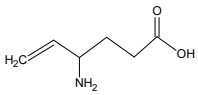


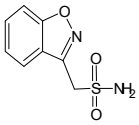
Trimethadione



Phensuximide



Vigabetrin



Zonisamide

Despite this, anticonvulsant drugs are estimated to be useful in treating 90% of all epileptic patients. However, all currently approved anticonvulsant agents have dosed related toxicity and idiosyncratic side effects. Additionally, many antiepileptic drugs induce xenobiotic-metabolizing liver enzymes resulting in complex and undesirable side effects. Despite the development of several new anticonvulsants, the treatment of epilepsy remains still inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases. Moreover, many antiepileptic drugs have serious side effects and lifelong medication may be required. Therefore, it is essential to search for newer chemical entities for the treatment. In the effort to get those agents, we have reported several heterocyclic compounds which have shown considerable anticonvulsant activities [14, 15].

Mechanism Of Anticonvulsant Drugs: A seizure is the clinical manifestation of a hyper excitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered— excitation predominates over inhibition. Effective seizure treatment generally augments inhibitory processes or opposes excitatory processes. Since the normal resting neuronal membrane potential is intracellular negative, inhibitory processes make the neuron more electrically negative, hyperpolarizing the membrane, while excitatory processes make the intracellular potential less negative or more positive, depolarizing the cell. On an ionic level, inhibition is typically mediated by inward chloride or outward potassium currents, and excitation by inward sodium or calcium currents. Drugs can directly affect specific ion channels or indirectly influence synthesis, metabolism, or function of neurotransmitters or receptors that control channel opening and closing. The most important central nervous system inhibitory neurotransmitter is gamma-amino-butyric acid (GABA). The most important excitatory neurotransmitter is glutamate, acting through several receptor subtypes. Excitatory neurotransmission mediated by calcium and sodium currents through glutamate receptors has been a tempting target for new AEDs, because these currents may contribute not only to seizure generation but also to neuronal damage from status epilepticus and stroke [16].

Pharmacokinetics: It mainly includes drug

absorption, distribution, metabolism and elimination/ excretion.

A. Absorption: Absorption is determined by route of intake. Most AEDs are available for oral administration, although some have formulations that are also available for intravenous, intramuscular or rectal administration. Most AEDs undergo complete or nearly complete absorption when given orally.

B. Distribution: Following absorption into the bloodstream, the drug is distributed throughout the body. Lipid solubility and protein binding affect CNS availability. Drugs can displace others from albumin and protein binding is responsible for many pharmacokinetic interactions between AEDs.

C. Metabolism: Most AEDs are metabolized in the liver by hydroxylation or conjugation. These metabolites are then excreted by the kidney. Most AEDs are metabolized by the P450 enzyme system in the liver. Different AEDs either induce or inhibit certain isoenzymes of this system and can result in changes of the pharmacokinetic properties of different medications. In general enzyme inducers decrease the serum concentrations of other drugs metabolized by the system and enzyme inhibitors have the opposite effect.

D. Elimination: Drug elimination rate is usually expressed as the biological half-life and is defined as the time required for the serum concentration to decrease by 50% following absorption and distribution. This changes for some drugs based on serum concentration. The half-life also determines the dosing frequency required for a drug to be maintained at a steady state in the serum. Most drugs are eliminated by the kidneys and dosage adjustments are required in cases of renal impairment.

Pharmacodynamic Interactions

Drug interactions based on pharmacokinetics, or "what the body does to the drug," must be distinguished from those based on Pharmacodynamic, or "what the drug does to the body." Pharmacodynamic effects include both wanted and unwanted drug effects on the brain and other organs. Ideally, drug combinations should produce additive or synergistic (supra-additive) therapeutic effects and sub-additive toxicities. Drug combinations with different mechanisms of action may help achieve this goal.

Chalcones and their derivatives show antiulcerative, anti-angiogenic, analgesic, anti-inflammatory, anticancer and antioxidant due to presence of very reactive vinylenic group but often they are cytotoxic in vitro. The presences of hydroxyl and phenyl group are responsible for antioxidant properties. Some chalconesderivatives show antimicrobial, anti-fungal and insecticidal activity. Some of chalcones derivatives are isolated with the anticanceractivity. [17]. Moreover, chalcones derivatives are also regarded as a new class of effective anti-TB candidates owing to their potential anti-TB activities. chalcones, like

isoniazid (INH), act by inhibition of the growth of bacteria by blocking lipid biosynthesis and/or additional mechanisms, which are one of the most attractive strategies for developing effective anti-TB agents [18].

Inflammation;

Inflammation (Latin, i*nflammo*,"I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants [19].

Inflammation is a protective immunovascular response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen [20].

Inflammation is tightly regulated by the body. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (eg. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g. gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation*, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process [21].

Inflammation is not a synonym for infection. Infection describes the interaction between the action of microbial invasion and the reaction of the body's inflammatory defensive response - the two components are considered together when discussing an infection, and the word is used to imply a microbial invasive cause for the observed inflammatory reaction. Inflammation on the other hand describes purely the body's immunovascular response, whatever the cause may be. But because of how often the two are correlated, words ending in the suffix *-itis* (which refers to inflammation) are sometimes informally described

as referring to infection. For example, the word urethritis strictly means only "urethral inflammation", but clinical health care providers usually discuss urethritis as a urethral infection because urethral microbial invasion is the most common cause of urethritis [22].

On the other hand, It is useful to differentiate inflammation and infection as there are many pathological situations where inflammation is not driven by microbial invasion - for example, atherosclerosis, type III hypersensitivity, trauma, ischaemia. There are also pathological situations where microbial invasion does not result in classic inflammatory response - for example, parasitosis, eosinophilia.

Causes of inflammation [22]:

Physical:

-Burns
-Frostbite
-Physical injury, blunt or penetrating
-Foreign bodies, including splinters, dirt and debris
-Trauma
-Ionizing radiation

Biological:

-Infection by pathogens
-Immune reactions due to hypersensitivity
-Stress

Chemical:

-Chemical irritants
-Toxins
-Alcohol

Types of inflammation:[24]

- Appendicitis
- Bursitis
- Colitis
- Cystitis
- Dermatitis
- Phlebitis
- RSD/CRPS
- Rhinitis
- Tendonitis
- Tonsillitis
- Vasculitis

Anti-inflammatory:

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation or swelling [25]. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Non-steroidal anti-inflammatory drugs (NSAIDs), alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own, COX enzyme synthesizesprostaglandins, creating inflammation. In whole, the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain [26].

Some common examples of NSAIDs are: aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors are not classified together with the traditional NSAIDs even though they presumably share the same mode of action.

On the other hand, there are analgesics that are commonly associated with anti-inflammatory drugs but that have no anti-inflammatory effects. An example isparacetamol, called acetaminophen in

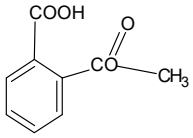
the U.S. and sold under the brand name of Tylenol. As opposed to NSAIDs, which reduce pain and inflammation by inhibiting COX enzymes, paracetamol has as early as 2006 been shown to block the reuptake of endocannabinoids [27] which only reduces pain, likely explaining why it has minimal effect on inflammation.

Chemical Classification:[28]

Depending upon the chemical structure Non-steroidal anti-inflammatory drugs (NSAIDs) can be chemically classified as:

Salicylates:

- Aspirin (acetylsalicylic acid)



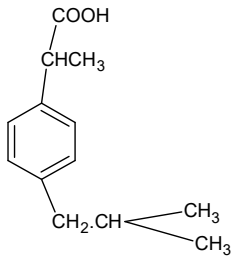
-Diflunisal (Dolobid)

-Salicylic acid and other salicylates

-Salsalate

Propionic acid derivatives:

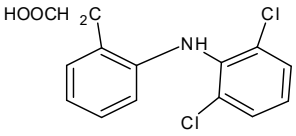
-Ibuprofen[29]



-Dexibuprofen
-Naproxen
-Fenoprofen
-Ketoprofen
-Dexketoprofen
- Flurbiprofen
- Oxaprozin
-Loxoprofen

Arylacetic acid derivatives:

- Diclofenac

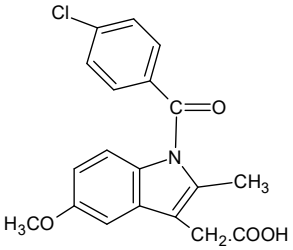


-Tolmetin

- Fenclofenac

Indole& related compounds:

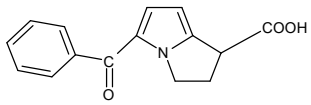
- Indomethacin



-Sulindac

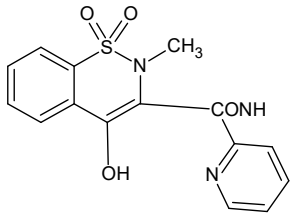
Pyrrolo-Pyrrole derivatives:

-Ketorolac



Enolic acid (Oxicam) derivatives:

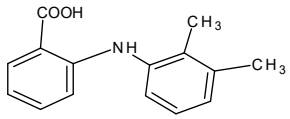
- Piroxicam



- Meloxicam
- Tenoxicam
- Droxicam
- Isoxicam

Anthranilic acid derivatives (Fenamates):

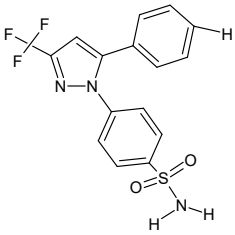
- Mefenamic acid



- Meclofenamic acid
-Flufenamic acid
- Tolfenamic acid

Selective COX-2 inhibitors (Coxibs):

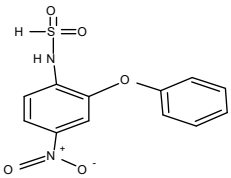
-Celecoxib[30]



-Rofecoxib[8]
- Valdecoxib[9]
- Parecoxib
- Lumiracoxib
- Etoricoxib
- Firocoxib

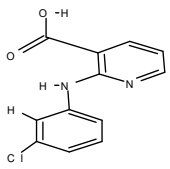
Sulfonanilides:

- Nimesulide



Others:

- Clonixin



Mechanism Of Action:

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2)isoenzymes. This inhibition is competitively reversible (albeit at varying degrees of reversibility), as opposed to the mechanism of aspirin, which is irreversible inhibition [31, 32].

COX catalyzes the formation of prostaglandins and thromboxane from arachido nic acid (itself derived from the cellular phospholipid bilayer byphospholipaseA_2). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated byJohn Vane (1927–2004), who received a Nobel Prize for his work.

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs [33-36]. When non-selective COX-1/COX-2 inhibitors, NSAIDs have been studied in various assays to understand how they affect each of these enzymes. While the assays reveal differences,

unfortunately different assays provide differing ratios [37-39]

Microorganism

A microorganism or microbe is an organism that is microscopic (usually too small to be seen by the naked human eye). Microorganisms are very diverse; they include bacteria, fungi, archaea, and protists; microscopic plants (green algae) and animals such as plankton the planarian and the amoeba. Robert Koch (1843-1910) defined the principles of infectious diseases, namely, that a microbe causing disease in one animal when transferred to another animal produces the same disease (Koch's postulate). Koch also identified *Mycobacterium tuberculosis*, *Vibrio cholera* [40-42].

Broadly, all microbes that can grow in the absence of oxygen are called anaerobic bacteria. They include clostridia, a spore-bearing anaerobe, and Gram-negative bacteria like bacteroides and fusobacteria. Microbes that require oxygen to grow are called aerobic bacteria. Those that grow in the presence of some oxygen (but not a lot) are called microaerophilic; they include *E. coli, neisseria, haemophilus* and others. Gram (1853-1938) classified all bacteria by the colour they take with the Gram's stain. Those that take a blue colour (Gentian violet) are called Gram-positive, and those that take the red stain (eosin) are called Gram-negative [43-44]

Infection

Diseases caused by bacteria, viruses, fungi and other parasites are major causes of death, disability, social and economic disruption for millions of people.[4] Infectious diseases raise awareness of our global vulnerability, the need for strong health care systems and the potentially broad and borderless impact of disease [45].

The human body exists in a state of dynamic equilibrium with microorganism. In a healthy individual this balance is maintained as peaceful co-existence and lack of disease. But sometimes, micro-organisms cause an **infection** or a **disease.**

Bacteria

During the ninethteeth century, the French scientist Louis Paster and German physician demonstrated the roll of bacteria as pathogens the discovery of compound produce by bacteria and fungi have shown their the lethal effect to other bacteria led to development of antibiotics.

Bacteria are free living, microscopic, unicellular organism capable of performing all the essential functions of life i.e. growth, metabolism and reproduction .They possess both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and lack of chlorophyll [46]. Bacteria have been placed in a kingdom separate from the animal and plant kingdoms.

Type of Bacteria

Scientist use various system for classifying bacteria based on different, shapes, dependence on oxygen and by staining techniques.

Aerobic and anaerobic Bacteria:-

Bacteria can be classified according to need of the oxygen to survive. As aerobic bacteria require

oxygen and anaerobic do not requires oxygen to survive

eg. Bacillus Anthrax aerobic , Clostridium titani anaerobic

Classification by shapes [47]

Shapes	Description	Examples
Cocci	Cocci (berry) are spherica or oval shapes	Staphylococcus Aureus
Bacilli	Bacilli are rod shapes cells.	Clostridium tetani
Vibrios	Vibrius are comma shaped curved rods.	Vibrios cholera

Autotrophic and Heterotrophic Bacteria:-

All bacteria require carbon for growth and reproduction bacteria called autotrophes get their carbon from carbondioxide and heterotrophes from organic nutrient.

Gram Positive and Gram Negative:-

Bacteria can be classify by the Gram staining

Disease caused by pathogenic Bacteria:

Sr. no	Disease	Causative microorganism
1	Diphtheria	Corynebacteriumdiphtheriae
2	Tuberculosis	Mycobacterium Tuberculasis
3	Leprosy	Mycobacterium leprae
4	Tetanus	Clostridium Tetanus
5	Diarrhea	E.coli
6	Typhoid fever	SalemonellaTyphi
7	Gonorrhea	Neisseria gonorrhoeae

techniques which is identified as Gram positive and Gram Negative after staining they stains purple and pink respectively [48]. Eg. S. Aureus(Gram + ve), E.coli(gram -ve).

Some of the diseases caused by bacteria's are tuberculosis, cholera, syphilis, typhoid fever and tetanus.

Antibacterial Agents

Anti microbial agents can be divided according to their mechanism of action.

a. Agents that inhibit bacterial cell wall synthesis.

b. Agents that interfere with DNA-RNA synthesis.

c. Anti metabolites.

d. Agents that interfere with protein synthesis.

Agents that inhibit bacterial cell wall synthesis:

This includes B-lactamase antibiotics, like Ampicilin and Cephalosporines B-lactamase inhibits D-alanyl-D-alanine transpeptidaseactivity by acylation,forming stable esters with opened lactum ring attached to hdroxyl group of the enzymes active site [49].

Agents that interfere with protein synthesis.

This class includes, Tetra cyclones, which block and binds aminoacyl receptor site of tRNA, Chloramphinicol, and Erythromycines, binds p-sites of the 50S ribosomal subunit [50] and inhibit translation.

Agents that interfere with DNA-RNA synthesis.

Quinolones, are bactericidals and they inhibit DNA gyrasesynthesis,eg. Ciprofloxacine, norfloxacine, sparfloxacine.

Sulphonamides inhibit microbial growth by inhibiting P-aminobenzoic acid (PABA) invoved in folic acid synthesis.

Fungi

Fungi are heterotropic organism, they don't form embryos. Fungi are eukaryotic chemo - organiotropic organism that has no chlorophyll. They posses rigid cell wall containing chitin, manoproteins[50], glucans, and polysaccharides. They divide asexually and sexually or by both process. They may be uni or multi cellular. Fungi are typically aerobic.

The discovery that some infectious diseases could be attributed to fungi actually preceded the Pioneerring work of Pasteur & Koch with pathogenic bacteria by several years. Two microbiologist Schonlein&Gruby studied the fungas Trichophyton Schoenleinni reported the yeast like micro-organism responsible for the thrush *(candida albicans*) Gruby isolated the fungus responsible for favusanpotatoslices,rubbed it on the head of a child & produced a disease .

Classes of Fungi

- Yeast
- Yeasts like fungi
- Moulds
- Dimorphic fungi

Sr.No	Disease	Causative organism
1	Aspergillosis	Aspergillusniger
2	Candidasis	Candida albicans
3	Tineaniger	Tina nigera
4	Mycetomas	Acremoniumfaliciforme

Antifungal Agents:-

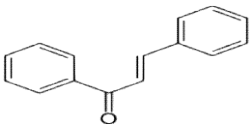
Fungi cause a range of illnesses (mycoses) ranging from the chronic to the serious. These mycoses can manifest themselves in a variety of ways. Infections can be superficial, that is situated at or close to the surface of the skin or systemic which means they can affect the body as a whole, rather than individual parts or organs.

Diseases such as athlete's foot (Tineapedis), 'jock' itch (Tineacruris), Tineamanus (infection of the hand), thrush (oral and vaginal), and onchomycosis (affecting the nails) are examples of superficial infections caused by the dermatophytes from the *Trichyphyton microsporum, C. albicans* and *Epidermophyton species*[46,50]. 'Ringworm' (Tineacorporis) is used as a general term for a fungal infection of the skin, in particular those of the scalp and feet. These infections are contagious, and cause intense itching. One or more of these organisms causes them.

An important aspect to consider when developing treatments for mycoses is that fungi are eukaryotic. That is to say they have a nucleus within the cell containing the all-important nucleic acids. In very simplistic terms this means that some of the biochemistry regulating fungi turns out to be very similar to animal cells. They are therefore unlike the prokaryotic bacteria, which do not have a cell nucleus. This can in turn pose potential problems with toxicity.For many enzymes in a fungus there are related enzymes performing

the same transformations in the human cell [44, 50]. If we want to target one of these enzymes with drug then absolute potency may not be as important as the difference in potency of our drug towards the different forms of the enzyme.

Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. Alternative names for chalcone include benzylideneacetophenone, phenyl styryl ketone, benzalacetophenone, *β*-phenylacrylophenone, *γ*-oxo-*α*,*γ*-diphenyl-*α*-propylene, and *α*-phenyl-*β*-benzoylethylene.



Chalcone

Chalcones can be prepared by an aldol condensation between benzaldehyde and acetoph enone in the presence of sodium hydroxide as a catalyst. This reaction can be carried out without any solvent as a solid-state reaction [51]. The reaction between substituted benzaldehydes and acetophenones can be used as an example of green chemistry in undergraduate education. In a study investigating green syntheses, chalcones were synthesized from the same starting materials in high-temperature water (200 to 350 °C).

CONCLUSION

Every year approximately 250000 new cases are added to this figure. Epilepsy is a brain disorder in which a person has repeated seizures (convulsions) over time. Seizures can result from exposure to lead, carbon monoxide, and many other poisons. They also can result from exposure to street drugs and from overdoses of anti-depressants and other medications. . The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the primary focus. Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. . Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers, and in the treatment of neuropathic pain. Drug or vagal nerve stimulator therapy is the most widely effective mode for the treatment of patients with epilepsy. Since the normal resting neuronal membrane potential is intracellular negative, inhibitory processes make the neuron more electrically negative, hyperpolarizing the membrane, while excitatory processes make the intracellular potential less negative or more positive, depolarizing the cell. Most AEDs are metabolized by the P450 enzyme system in the liver. Different AEDs either induce or inhibit certain isoenzymes of this system and can result in changes of the pharmacokinetic properties of different medications. Drug

combinations with different mechanisms of action may help achieve this goal.Chalcones and their derivatives show antiulcerative, anti-angiogenic, analgesic, anti- inflammatory, anticancer and antioxidant due to presence of very reactive vinylenic group but often they are cytotoxic in vitro. Inflammation is tightly regulated by the body. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (eg. bacteria) and compromise the survival of the organism. COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. They include clostridia, a spore-bearing anaerobe, and Gram-negative bacteria like bacteroides Broadly, all microbes that can grow in the absence of oxygen are called anaerobic bacteria and fusobacteria. An important aspect to consider when developing treatments for mycoses is that fungi are eukaryotic. That is to say they have a nucleus within the cell containing the all-important nucleic acids.

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