Chapter 1
Introduction

1. INTRODUCTION

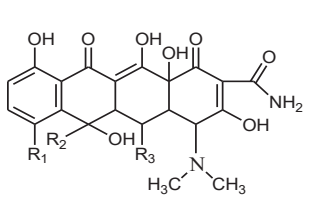
1.1 Antibiotics and their development:

The fast and widespread evolution of antibiotic resistance pose a grave threat to therapy of many bacterial infections and necessiciate imperative and scrupulous efforts to develop next generation of antibiotics. The availability of complete microbial genome sequence has led to devise concerted strategy to look at novel antibacterials. Nevertheless, in spite of the identification of many new potential drug targets, novel antimicrobial agents have been sluggish to emerge from these efforts [Schmid *et al*. 2004]. Multidrug resistance (MDR) to antibiotics is a problem that has long plagued public health [Singh *et al*. 2012]. Extremely resistant bacteria such as methicillin- resistant *Styphlococoous aureus* (MRSA) and Vancomycin resistant *enterococci* account for a soaring percentage of hospital acquired infections [Martins *et al*. 2011]. However, the significant technological advances in the past decade, in the fields of genomics, molecular biology, high throughput screening and structural biochemistry have led to essentially new standards in the quest for novel antimicrobial agents [Learner *et al*. 2002]. Yet, in the past forty years, only two structural types i.e. Daptomycin and Linezolid have been introduced to the clinical use following their discovery using empirical screening methods [Simmons *et al*. 2010]. Therefore, the discovery of drugs with novel mode of action will be imperative to meet the threats caused by the emergence of resistance.

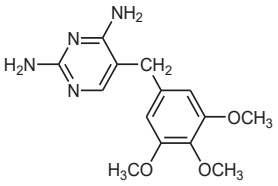
One important qualitative difference between the microbial and mammalian cells is the presence of a cell wall in the former. In consequence, enzymatic pathways leading to the formation of the cell wall are potential targets for antimicrobial drugs. One such target enzyme, i.e. L-glutamine: D-fructose-6-phosphate amidotransferase, known under the trivial name of glucosamine-6-phosphate synthase, is important for antimicrobials [Milewski *et al*. 1988]. Glucosamine-6-phosphate (GlcN-6-P) synthase is a ubiquitous enzyme and its activity has been detected in a number of organisms and tissues. Obviously, glucosamine-6-phosphate, the product of this enzyme, is indispensable for fungi as well as for bacterial cells. The product GlcN-6-P is a precursor of uridine diphospho-*N*-acetyl glucosamine from which other amino sugar-containing molecules are derived. One of these products, *N*-acetyl glucosamine, is an important constituent of the peptidoglycan layer of bacterial cell wall and fungal cell wall chitin. It has shown that even a short-time inactivation of GlcN-6-P synthase in fungal cells is lethal for the pathogen [Milewski *et al*. 2002].

Since the introduction of antibiotics into the market more than 70 years ago, antibiotics

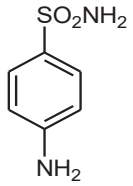
have continued to contribute immensely to human health in combating infections. Antibiotics have been losing efficiency as a consequence of the remarkable adaptability of bacteria as well as their uncontrolled and inappropriate uses that has resulted in a dramatic increase in resistant bacteria. In the period between the 1930s and 1960s, arsenals of new antibiotic classes were introduced a majority of which are still employed in current clinical practice. Nearly four decades elapsed before two new classes of antibiotics (oxazolidinone and lipopeptides) entered into the market in 2000 and 2003, drugs efficient against Methicillin and/or Vancomycin-resistant Gram-positive bacteria.



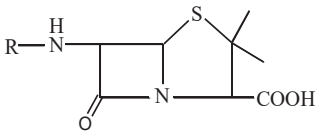
1.Substituted Tetracycline



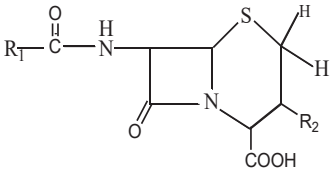
2.Trimethoprim



3.sulphanilamide



4.Substituted 6-aminopenicillanic acid
(Penicillin)



5.Substituted 7-aminocephalosporanic acid
(Cephalosporin)

Few conventional antibiotics

The reasons behind the innovation gap are decreasing attention to the antibacterial research within the pharmaceutical industry and the increased time, cost and complications involved in the drug development and approval process, resulting in decreased return on investment. Not surprisingly, most of the antibiotics have come from a small set of molecular scaffolds whose functional lifetimes have been prolonged by cycles of synthetic adaptations. [Livermore *et al*., 2011].

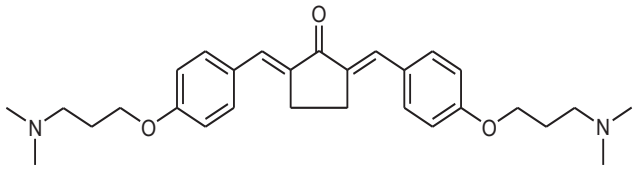
Antibiotics have always been considered as one of the wonder discoveries of the 20th century. This is true, but the real wonder is the rise of antibiotic resistance in hospitals, communities, and the environment concomitant with their use. The extraordinary genetic capacities of microbes have benefitted from man's overuse of antibiotics to exploit every source of resistance genes and every means of horizontal gene transmission to develop multiple mechanisms of resistance for each and every antibiotic introduced into practice clinically. To achieve complete restitution of therapeutic applications of antibiotics, there is a need for more information on the role of environmental microbiomes in the rise of antibiotic resistance. In particular, creative approaches to the discovery of novel antibiotics and their expedited and controlled introduction to therapy are obligatory. The successful

use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic, and viral infections and for treatment of chronic diseases such as cancer and diabetes. A wide range of biochemical and physiological mechanisms may be responsible for resistance. In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and dissemination of resistance cannot be overemphasized, and the lack of basic knowledge on these topics is one of the primary reasons that there has been so little significant achievement in the effective prevention and control of resistance development. Most international, national, and local agencies recognize this serious problem. Many resolutions and recommendations have been propounded, and numerous reports have been written, but to no avail.

The discovery of these infectious agents in the late 19^{th} century stimulated the search for appropriate preventative and therapeutic regimens; however, successful treatment came only with the discovery and introduction of antibiotics half a century later. Antibiotics have revolutionized medicine in many respects, and countless lives have been saved; their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearance of resistant strains. The treatment for infectious diseases still remains exigent quandary, despite the availability of novel antimicrobial agents; still there is growing attention in this field. Many compounds have been synthesized with this aim but their clinical use has been marred by relatively high toxicity, bacterial resistance and/or lack of desired pharmacokinetic properties.

1.2 Curcumin as antimicrobial agent

Curcumin has been reported for the treatment of bacterial infections through inhibiting the bacterial endotoxin-induced cytokines secretion, thereby directly suppressing pathogen cell growth. *In vitro* antibacterial activity of mono-carbonyl analogues of curcumin showed that heterocycle or long-chain substituents enhance the activity of curcumin analogues. Compounds **6**, **7**, **8**, **9** and **10** have shown remarkable *in vitro* antibacterial activity against the ampicillin-resisted *Enterobacter cloacae* [Liang *et al*. 2008]. Curcumin analogues inhibit *Pseudomonas aeruginosa* (PAO1) virulence factors such as biofilm formation, pyocyanin biosynthesis, elastase/protease activity, and acyl homoserine lactone (HSL) production.



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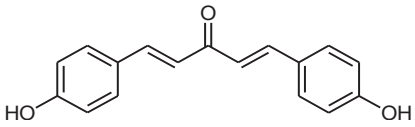

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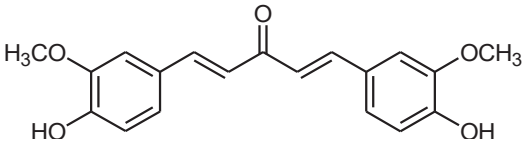

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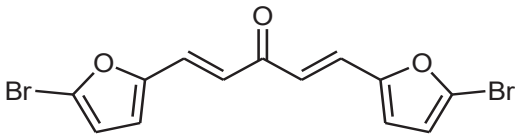

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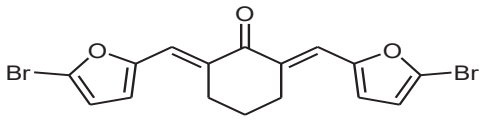


10.

Various mono-carbonyl analogues of curcumin

In addition, transcriptome analysis of curcumin treated PAO1 revealed down regulation of 31 quorum sensing (QS) genes. The effect of curcumin on multiple targets such as virulence, QS, and biofilm initiation makes curcumin a potential supplemental molecule for the treatment of *P. aeruginosa* infections. [Rudrappa *et al*. 2008]

1.3 Anti-malarial drugs and their development

Malaria has been a major cause of morbidity and mortality in developing countries, particularly in Sub-Saharan Africa and South Asia. The global malaria situation is increasingly being challenged owing to lack of credible malaria vaccine and the emergence of drug resistance to most of the available antimalarials. There is an urgent demand for search of novel generation of drugs. Most severe malaria is caused by the

blood-borne apicomplexan parasite *Plasmodium falciparum* occuring in children in sub-Saharan Africa. The two most widely used anti-malarial drugs, Chloroquine (CQ) and Sulphadoxine-Pyrimethamine (SP) are failing at an accelerating rate in most malaria-endemic regions with consequent increases in malaria-related morbidity and mortality [David *et al.* 2004]. To combat malaria, new drugs are desperately needed, but traditional methods for drug development have provided few drugs to the treat disease of developing world.

In this challenging situation, there are some reasons for optimism. First, the determination of the genome sequence of *P. falciparum* offers a multitude of potential drug targets and second, advances in malaria genetics offer improved means of characterizing potential targets. Third, the recent increased participation of pharmaceutical companies in the antimalarial drug discovery and development process offers hope for the development of new affordable drugs. The development of resistance by the parasite against first line and second line antimalarial drugs has underscored the importance to develop new drug targets and pharmacophores to treat the disease. The absence of a vaccine for protection has made the situation rather serious. With the availability of increased philanthropic support and recent advances in our knowledge of parasite biology as well as the availability of the genome sequence provide a wide range of opportunity for malaria research, a variety of drug targets and candidate molecules are now available for further development. However, the success rate of a candidate molecule to become a drug is very low and it does become necessary to start with a large basket, identified on a rational basis [David *et al.* 2004].

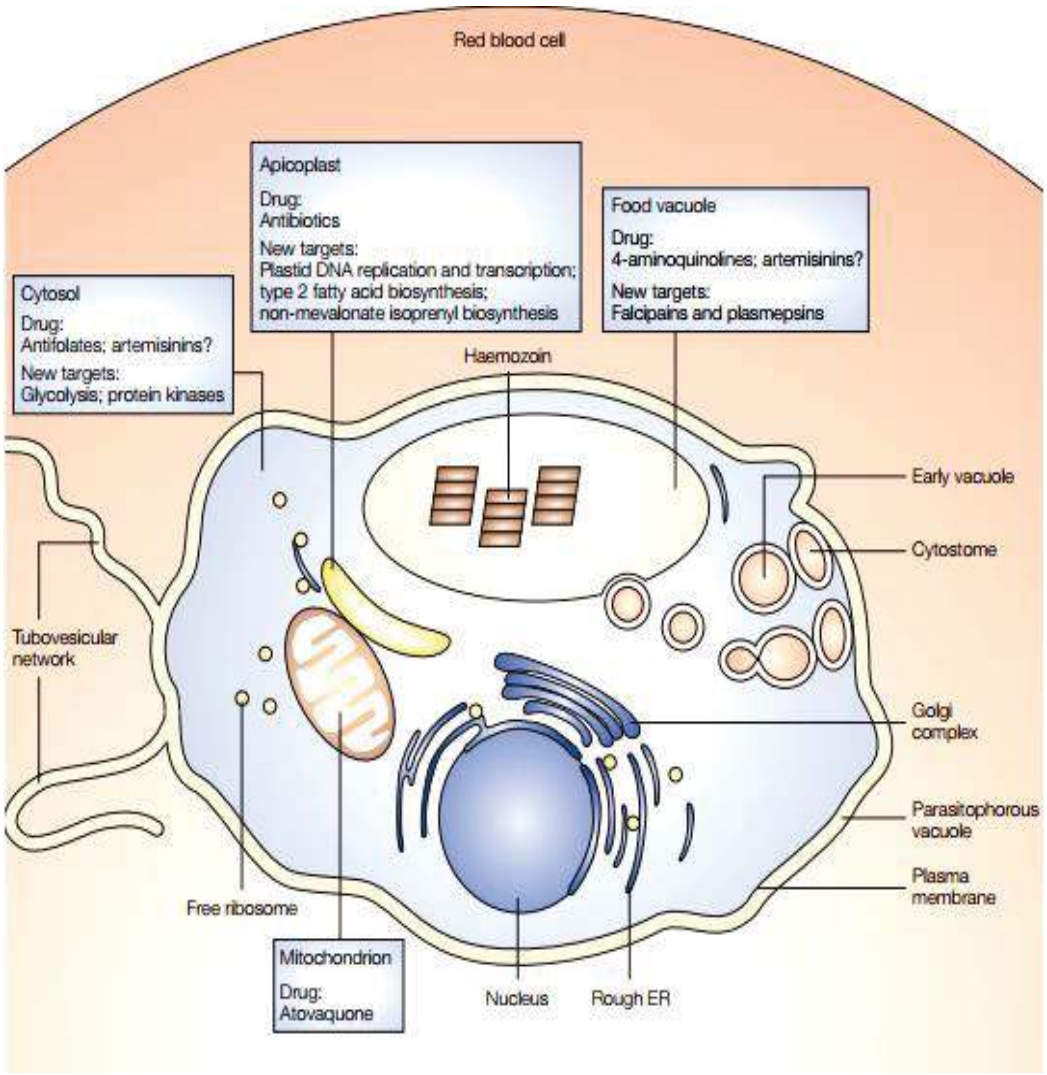


Fig.1.1 Representation of an intra-erythrocytic *Plasmodium falciparum* trophozoite, highlighting key parasite intracellular compartments and the site of action of some of the major classes of antimalarial drugs [David *et al*. 2004].

1.4 New Targets for Anti-malarial Drugs

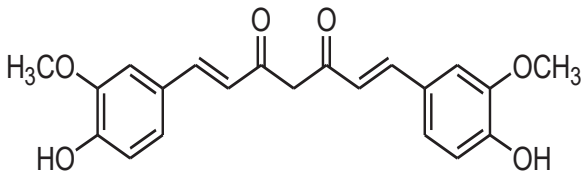
The most innovative approach to chemotherapy is the identification of new targets and subsequent discovery of compounds that act on these targets. Progress towards the characterization of the biology of malaria parasites has been stimulated by the development of technology to disrupt plasmodial genes. The readily accessible genome sequence facilitates genomic approaches to drug discovery, although the more difficult and risky biochemical and parasitological validation of putative drug targets remains essential and typically limits progress [Padmanaban *et al.* 2007].

Table 1.1. : Targets and available therapeutic compounds

Target Location	Pathway/ Mechanism	Target Molecule	Examples of therapies	
			Existing therapies	New compounds
Cytosol	Folate metabolism	Dihydrofolate reductase	Pyrimethamine, Proguanil	Chlorproguanil
		Dihydropteroate synthase	Sulphadoxine, Dapsone	-
	Glycolysis	Thymidylate synthase	-	5-fluorocrotate
		Lactate dehydrogenase	-	Gossypol derivatives
		Peptide deformylase	-	Actinonin
	Protein synthesis	Heat- shock protein 90	-	Geldanamycin
	Glutathione metabolism	Glutathione reductase	-	Enzyme inhibitors
	Signal transduction	Protein kinase	-	Oxindole derivatives
	unknown	Ca^{2+}-ATPase	Artemisinins	-
Parasite membrane	Phospholipid synthesis membrane transport	Choline transporter	-	G25
		Unique channels	Quinolines	Dinucleoside dimers
		Hexose transporter	-	Hexose derivatives
Food vacuole	Haemoglobin polymerization	Haemozoin	Chloroquine	New quinolones
	Haemoglobin hydrolysis	Plasmepsins, Flacipains	-	Protease inhibitors
	Free radical generation	Unknown	Artemisinins	New peroxides
Mitochon-drion	Electron transport	CytochromeC oxidoreductase	Atovaquone	-
Apicoplast	Protein synthesis	Apicoplast ribosome	Tetracyclins	-
	DNA synthesis	DNA gyrase	Quinolones	-
	Transcription	RNA polymerase	Rifampin	-
	Type II fatty acid bio-synthesis	FabH/Fabl/Plasmodium falciparum enoyl-ACP reductase	-	Thiolactomycin, Triclosan
	Isoprenoid synthesis	1-deoxy-o-zylulose5-phosphate reductoisomerase	-	Fosmidomycin
	Protein farnesylation	Farnesyl transferase	-	Peptidomimetics
Extra-celular	Erythrocyte invasion	Subtilisin serine protease	-	Protease inhibitors

1.5. Curcumin as Antimalarial

Curcumin has been used in traditional medicines as household remedy for the treatment of various diseases, including biliary disorders, anorexia, cough, hepatic disorders, rheumatism and sinusitis. Turmeric is reported as a component of traditional remedies for malaria and fever in India. Curcumin, a polyphenol extracted from the roots of *Curcuma longa* L., is reported to exhibit multiple biological activities and pharmacological actions. Recent studies have indicated that curcumin inhibits Chloroquine-sensitive (CQ-S) and Chloroquine-resistant (CQ-R) *P. falciparum* growth. Many of the synthetic analogues of curcumin have expanded its antimalarial activity as they have shown more effective inhibition of *P. falciparum* growth than curcumin. Similar to Artemesinin (ART), PfATP6, also known as PfSERCA or PfATPase6, is a calcium ATPase gene encoded by the malaria parasite *Plasmodium falciparum* could be possible target for curcumin action. New alternative of ART-based combination therapies (ACTs) demonstrate a better overall efficacy and delay the emergence of resistance. However, their cost, adverse drug reaction and pharmacokinetic mismatch of each drug of the combination presents gloomy picture of present alternatives of ACTs.

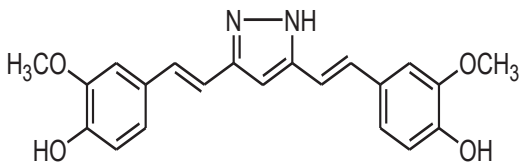


11.

Structure of curcumin

Studies with animal models have indicated that a combination therapy with ART and curcumin can add a new dimension to malaria therapy in terms of its potential to prevent parasite recrudescence and relapse in *P. falciparum* and *P. vivax* malaria as well as protecting against cerebral malaria. Both these partner drugs have short half-lives and no resistance is known to curcumin.

Pyrazole analogues of curcumin exhibited seven fold higher antimalarial potency against CQ-S strains and nine fold higher antimalarial potency against CQ-R strains. Recent, study on mono carbonyl analogues of curcumin indicated their safety towards mammalian cells. Considering the selectivity index for cytotoxicity (Vero cell) to antimalarial activity, it was demonstrated that all the monocarbonyl analogues of curcumin are non toxic [Kumar *et al*. 2013].



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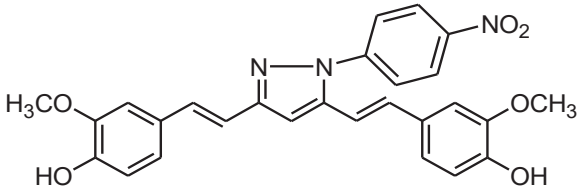

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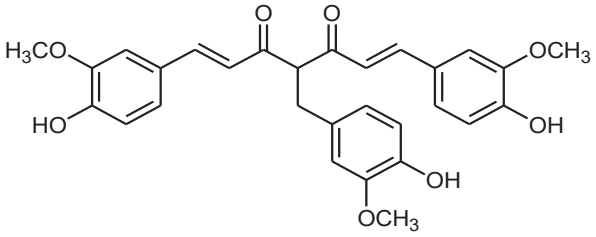

14.

Chemical structures of potential curcumin analogues.

1.6. Malaria burden in India

In the 1950s and early 1960s, a major global initiative of World Health Organization (WHO) to eradicate malaria brought malaria under firm control in India and almost on the verge of eradication, but a reverse followed in the mid-1960s until the mid-1970s; the disease staged a comeback with vengeance. In the 1980s, new malaria ecotypes developed from environmental and developmental impact and were followed by outbreaks and epidemics in the1990s. There are vast lands inhabited by ethnic tribes in Madhya Pradesh, Chattisgarh, Jharkhand, Orissa, and the entire northeastern region, where malaria has remained deeply entrenched, *P. falciparum* preponderance is persistent, and asymptomatic burden in these areas is not known. The emergence of resistance to Chloroquine in *P. falciparum* in many pockets of the country and reports of reducing sensitivity in *P. vivax* are major causes of concern. In some areas in the northeastern region, even foci of multi-drug–resistant *P. falciparum* have been found. Alternate therapies such as Mefloquine and Artemisnin derivatives or combination therapies are expensive, since they have been selectively introduced in the control program, would require constant monitoring for their judicious use and to observe emergence of resistance against them.

The changing clinical manifestations with multi-organ involvement in *P. falciparum*, emerging trends of complications in *P. vivax* malaria, and burden of malaria in pregnancy are other important issues that merit attention and formulation of suitable intervention strategies. Historically, *P. vivax* has been suspected to impose a significant burden of mortality, resulting from its interaction with other diseases and conditions. The malaria-specific mortality gap needs to be bridged. While the reported number of deaths is ~1000, the actual mortality caused by malaria is many folds higher. Even the medical certification of cause of death (MCCD) report, which covers both rural and urban areas, extensively suffers from serious limitations because of non-reporting of mortality by some key malaria-affected states and also due to the overall incomplete medical certification of deaths and attribution of specific cause of death.

Health planners and administrators need estimates of the true burden of malaria for allocation of much needed resources for interventions. The current reported incidence of ~2 million/year in India at best reflect a trend, and given the gaps identified in various studies, the actual incidence is definitely far more than presently known. The reasons attributed to such a gap are deficiencies in coverage, collection, and examination of blood smears and reporting systems. Moreover, in India, the government health sector, which provides free or highly subsidized health care, caters to the needs of 20% of the population, mainly in rural areas, whereas the rest of the population seeks health care in the private sector as their first point of contact, where the bulk of malaria is generally treated empirically. The clinically treated cases never or rarely find place in the official statistics. This gap needs to be bridged to build burden estimates. Coupled with this, there is the likelihood of a sizable population acting as asymptomatic carriers of plasmodial infection, particularly in malarious areas inhabited by ethnic tribes in India, where meso to hyperendemic conditions exist. In such areas, inaccessibility and insurgency seem to be major causes of deficient routine surveillance services [*Kumar et al.* 2007].

1.7. Curcumin ring and its biological activities.

Polyphenol curcumin [diferuloylmethane; 1, 7-bis-(4-hydroxyl 3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione], the main active ingredient of turmeric, is a yellow colour compound found in the rhizomes of *Curcuma longa* (Family: Zingiberaceae) [Anderson *et al.* 2000]. Turmeric, a spice commonly used in India, better known as ‘‘Indian solid gold’’ due to its numerous therapeutic activities, pharmacological safety and colour. The emerging role of curcumin and its analogues in different clinical trials has given us chance

to rethink on its synthetic analogues. The low side effect of curcumin as found in human trial has boosted morale for delving deep into synthesis of novel analogues for treatment of various diseases. The biological effects of curcumin has been widely studied for its anti-inflammatory [Hong *et al*. 2004], antiangiogenic [Bhandarkar *et al*. 2007], anti-oxidant [Sugiyama *et al*. 1996], antimicrobial [Negi *et al.* 1999], [Singh *et al.* 2002] and anticancer [Huang *et al.* 1991] activities. Pyrazole analogues of curcumin have shown seven-fold higher anti-malarial activity against Chloroquine sensitive (CQ-S) and nine-fold higher anti-malarial activity against Chloroquine resistant (CQ-R) *Plasmodium falciparum* strains [Mishra *et al*. 2008].

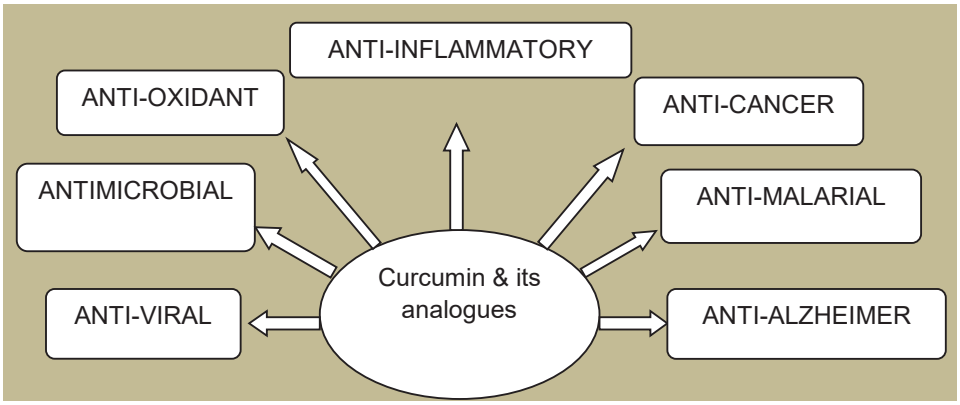

Fig. 1.2 Biological effects of curcumin and its analogues

Curcumin has also been reported to inhibit β-secretase and acetylcholinesterase, and play a pivotal role in amyloid-β-protein (Aβ) aggregation and Aβ-induced inflammation [Hamaguchi *et al*. 2010]. The promising role of curcumin in pathophysiology of Alzheimer's diseases has widely drawn researcher's attention. It has shown remarkable role in prevention of various types of cancer including lymph, gastrointestinal, genitourinary, breast, ovarian, head and neck cancers. It modulates growth of tumour cells through regulation of multiple cell signalling pathways including cell proliferation (Cyclin D1, c-myc), cell survival (Bcl-2, Bcl-XL, Cflip, XIAP, c-IAPI), caspase activation (caspase-8, 3, 9) and protein kinase pathway (JNK, AKT and AMPK) [Ravindran *et al*. 2009]. Curcumin also acts as a scavenger of nitric oxide and inhibits cyclooxygenase-2 (COX-2), a pro-inflammatory mediator [Goel *et al*. 2001].

Resistance to antimalarial drugs results in unavoidable morbidity, mortality, and financial losses. Urgent measures are needed now to reduce the current and future burden of disease. There is essential requirement to develop a novel moiety to counter drug resistance against current line treatment for malaria.

1.8. Molecular docking

The field of molecular docking has emerged during the last three decades driven by the needs of structural molecular biology and structure-based drug discovery. It has been greatly facilitated by the dramatic growth in availability and power of computers, and the growing ease of access to small molecule and protein databases. The three dimensional structures known may be represented to show different views of the structures. [Morris *et al.* 1998; Morris *et al.* 1996] It is possible to superimpose one structure on another with complex molecular mechanics programs. The same approach is used to superimpose the three dimensional structure of a potential drug on its possible target site. This process, which is often automated, is known as docking. Molecular docking is used to predict the structure of the intermolecular complex formed between two molecules. The small molecule called Ligand usually interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of compounds. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. It also predicts the strength of the binding, the energy of the complex; the types of signal produced and calculate the binding affinity between two molecules using scoring functions. The most interesting case is the type protein-ligand interaction, which has its applications in medicine. The goal of automated molecular docking software is to understand and predict molecular recognition, both structurally, finding likely binding modes, and energetically, predicting binding affinity. Molecular docking is usually performed between a small molecule and a target macromolecule. The following are majorly used method for docking.

Lock and Key\Rigid Docking – In rigid docking, both the internal geometry of the receptor and ligand is kept fixed and docking is performed.

Induced fit\Flexible Docking - An enumeration on the rotations of one of the molecules (usually smaller one) is performed. Every rotation the surface cell occupancy and energy is calculated; later the most optimum pose is selected.

1.9. Quantitative Structure Activity Relationship (QSAR)

QSAR is a tool to find predictive relationship between quantitative descriptions, physicochemical properties of compounds and the response of biological system under considerations. QSAR explains reason for observed variations in biological activity relating to the change in substituent of the scaffold. After determining the lead, QSAR for that molecule will be established to improve the desired property and remove undesired

aspect of molecule. It provides quantitative description of the structural differences among series of chemical compounds of biological interest and the design of new & better therapeutic agents [Kubinyi *et al*. 1993].

Biological activity = f (physicochemical &/or structural parameters)

The QSAR equation is a linear model, which relates variations in biological activity to variation in the values of computed properties for a series of molecules. By QSAR approach, derived model describes the structural dependence of biological activity either by physicochemical parameters (Hansch approach) or by indicator variables encoding different structural features (Free Wilson) or by 3D molecular property profiles of compounds (CoMFA).

1.9.1 Role of QSAR in Drug Design [Nantasenamat *et al*. 2009]

1. QSAR is the only drug design method that allows one to make an accurate quantitative prediction of the potency of new analogues before their synthesis.
2. It is used for the designing of a series based on a lead molecule.
3. If one finds a QSAR of predictive value, it may happen that the optimum compounds have already been made and that none is appropriate for advanced testing. Thus, QSAR may help one to decide to stop synthesis in series and associated testing in animals.
4. It helps to find the mechanism of action of the molecule & their complement receptor mapping techniques.
5. Prediction is not single goal of a QSAR analysis. More often, general conclusions on the reduction of toxic properties, enhancing the selectivity, and optimizing the flexibility to pass the blood brain barrier and to avoid CNS side effects are more important for lead optimization. Thus, QSAR contributes indirectly to the development of a new drug.
6. QSAR aids in optimization of Biological activity, selectivity or spectrum of activity by adjustment of physicochemical property.

1.9.2 QSAR Descriptors [Timmerman *et al.* 2002]

Descriptor is a measure of a probable contribution of a group to a particular property of the parent drug with unique physicochemical properties, which are directly related to the intermolecular forces involved in the drug receptor interaction as well as to the transport and distribution properties of a drug. In this respect, hydrophobic polar electronic and steric properties are most important. On the basis of spatial characteristics, descriptors have been classified as:

1) 2D descriptors: They are calculated from purely atomic and connectivity properties, for instance, Molecular weight, Molecular balancing and Sum of atomic polarizabilities.

2) i 3D descriptors: The 'i' in i 3D descriptors use relative atomic 3D coordinates. Some examples are Potential Energy Volume and Water-Accessible Surface Area.

3) X 3D descriptors: The 'X' in X 3D is for external, X 3D use absolute atomic co-ordinates (i.e. aligned molecules are required), examples are the X, Y & Z co-ordinate dipole moments of the molecule, Common Overlap Volume and Receptor Interaction Energy.

The descriptors used in QSAR can be categorized as:

1) Conventional Descriptors:

- Thermodynamic descriptors.
- Electronic descriptors.
- Steric descriptors.

2) Non-Conventional Descriptors: These are advanced descriptors and used to explain the 3D electronic and steric characteristics of the molecules.

- MSA (Molecular shape analysis) descriptors.
- Spatial descriptors.

1.10 Matrixmetallo proteinase (MMPs)

Matrix metalloproteinases (MMPs) are a family of zinc-dependent, calcium-containing endopeptidases. The MMPs belong to a larger family of proteases known as metzincin superfamily. The research in the field of MMPs was initiated in 1962, when Gross and Lapiere reported the discovery of a collagenolytic enzyme involved in resorbing amphibian tadpole tails during metamorphosis. The enzyme was named interstitial collagenase (MMP-1) and became the first member of the MMP family. Since then, many other members of this family were found in vertebrates, including human, as well as in invertebrates and plants [Gomis-Ruth., 2003; Grossand & Lapiere., 1962].

1.10.1 Biological function

MMPs perform a variety of roles in living organisms. They are responsible for the tissue remodeling and degradation of many extracellular matrix (ECM) proteins, including collagens, elastins, gelatin, matrix glycoproteins and proteoglycan. More recently, it has also been recognized that they cleave many other peptides and proteins and perform other functions that may be independent of proteolytic activity. Physiological processes where

MMPs are involved include angiogenesis (formation of new blood vessels), apoptosis (process of programmed cell death), bone modeling or wound healing. [Vermaand *et al*. 2007; Overalland *et al.* 2002]

1.10.2. Role in pathological processes

Under normal physiological conditions, level of MMP expression and activity is very low. Transcription of these enzymes is tightly regulated by cytokines or growth factors, including transforming growth factors, interleukins (IL-1, IL-4, IL-6) or tumor necrosis factor alpha (TNF). Post-transcriptionally, MMP activity is controlled by interaction between zinc-containing catalytic site and N-terminal propeptide domain. When this balance between MMPs and their natural inhibitors is shifted towards enzyme expression and activity, increased tissue degradation occurs. Increased levels of MMP expression have been shown to be involved in a large number of pathological conditions, such as arthritis, Alzheimer's disease, cardiovascular disease, as well as cancer. MMPs have now been considered important pharmaceutical targets and extensive efforts have been put into the design of potential drugs based on MMP inhibition. [Sternlichtand & Werb, 2001]

1.10.3. Curcumin and MMPs

Curcumin, a natural yellow pigment of turmeric has become focus of interest with regard to its role in regulation of Matrix Metalloproteinases (MMPs). MMPs are metal dependent endopeptidases capable of degrading components of the extracellular matrix. MMP-9 (Gelatinase B) is one of the common matrix metalloproteinase that is associated with tissue destruction in number of disease states such as rheumatoid arthiritis, fibrotic lung disease, dilated cardiomyopathy, as well as cancer invasion and metastasis. MMP-9, in particular seems to be a key protease associated with tumor progression. Therefore, development of inhibitors of MMP-9 is an exigent task which can have therapeutic benefit for patients suffering from various cancers. [Gruber *et al.* 1996; Girija *et al*. 2010]