2.1.1 Origin of Staphylococcus: *Staphylococcus aureus* was first discovered as a cause of post-operative wound sepsis in the late 1870’s by Professor Sir Alexander Ogston of Aberden. In 1883, he named the cluster of grape-like (fig. 2) organisms as ‘Staphylococcus’ after the Greek word for a bunch of grapes and coccus means granule. It derives its specific epithet of aureus due to the golden colour of colonies grown on solid media (Ogston, A et al. 1984).

![Fig.2 Gram stain of *Staphylococcus aureus*](image)

2.1.2 *Staphylococcus aureus* resistance to antibiotics: Growing global public health threat

Antibiotic resistance has become a major public health problem on a global scale. The tendency to use antibiotics that promote the emergence of resistant pathogens is called antibiotic pressure, and there are many reports of resistance rising due to increased antibiotic use and falling after a reduction in use (McGowan, 1983). For example, serious infections due to staphylococci were curable with the discovery of Penicillin, but decades of misuse and over prescription of antibiotics created
resistance to Penicillin. S. aureus was a consequence of the acquisition of a plasmid, coding for Penicillinase, a Penicillin-hydrolysing enzyme, which is able to cleave the β-lactam ring and thus inactivate antibiotic molecule (Turlej et al., 2011). After that methicillin was used to treat infections caused by S. aureus, which was also became resistant to methicillin after some time (Boyce et al. 1997). The worldwide increase of Methicillin-resistant Staphylococcus aureus and the more recent emergence of vancomycin-intermediate S. aureus and vancomycin-resistant S. aureus strains had a major impact on antibiotic policies and prompted an active reaction from the pharmaceutical industry concerning the discovery and development of new antibiotics to combat these strains (Cornaglia and Rossolini, 2009).

2.1.3 the origin of MRSA & Resistance of Beta Lactam Drugs:

Methicillin-Resistant Staphylococcus aureus (MRSA) is a major cause of Hospital-Acquired infections that are becoming increasingly difficult to combat because of emerging resistance to all the current antibiotic classes.

The origins of the major MRSA clones are still poorly understood. Kreiswirth et al. proposed that all MRSA descended from a single ancestral S. aureus strain that acquired mecA (Blackwell, C.C. et al. 1975), but more recent studies show that some MRSAs are very divergent, implying that mecA has been transferred between S. aureus lineages (Kreiswirth, B et al. 1975, Musser, J.M et al. 1992).

Although the origin of MRSA is not fully understood, it is suspected that Methicillin-Susceptible S. aureus (MSSA) acquired the mecA gene through horizontal transfer form coagulase negative Staphylococci (Nita Chinan et al. 2004, Wn. S. Piscitelli et al. 1996). Subsequent evidence indicates that major MRSA clones repeatedly arose from successful epidemic MSSA Strains (Wieldere, C.H et al. 2001). Methicillin was introduced in 1959 to treat infections caused by Penicillin-Resistant
Staphylococcus aureus. In 1961, there were reports from the United Kingdom of S. aureus isolates that had acquired resistance to Methicillin (Wieldere Ch et al. 2001) and MRSA isolates were soon recovered from other European countries and other parts of the world (Wieldere, C.H et al. 2001).

2.1.4 Mechanism of B-Lactam Drugs Resistance in MRSA:

Fig. 3 Mechanism of Methicillin resistance by MRSA

1. A Staphylococcal cassette chromosome (SCCmec) type IV is incorporated not the S aureus genome, SCCmec type IV is typically found in CA-MRSA. 2. SCCmec IV encodes for the mecA gene. 3. Bacterium produces Penicillin-binding protein (PBP) 2a encoded by the mec A gene. 4. PBP2a protein is incorporated into the cell wall and has low affinity to bind Penicillin, which leads to Penicillin resistance. 5. Penicillin does not bind to the PBP2a protein and cannot inhibit the formation of peptidoglycan cross-links in the bacterial cell wall. This confirms the resistance of the organism to Penicillin.

Resistance to the Penicillinase-Resistance Penicillins is due to the presence of an altered Penicillin-binding Protein called PBP2a. This is due to the acquisition of a
chromosomal gene called mecA. PBP2a has a low affinity for all β-Lactam agents including Cephalosporins (Enright, M. C et al. 2001).

Resistance to Oxacillin and other Penicillinase-Resistant Penicillins may also be seen in S. aureus strains that lack the mecA determinant. In these cases, resistance is due to hyper production of β-lactamase enzymes, resulting in slow hydrolysis of the semi-synthetic Penicillins and borderline Methicillin/Oxacillin Resistance (Washington Winn et al. 2006).

2.1.5 Molecular and genetic factors pre-disposing to antimicrobial resistance in MRSA:

It is now recognized that coding for methicillin resistance in MRSA: is facilitated by the mecA gene, which is located on the staphylococcal cassette chromosome (SCC), a large mobile genetic element which differs in size and genetic composition from other strains of MRSA. The mechanism of resistance involves changes or defects brought about by mutation on mecA gene which result in modification to 78-kDa Penicillin binding protein 2a, which has a reduced affinity for β-lactam antibiotics that is able to mediate essential cell wall construction when β-lactam-susceptible PBPs have been inactivated (Hartman and Tomasz, 1986). The result of the event is that it renders the organism resistant to β-lactams and other antibiotics with a similar target site. In addition, other antibiotic resistant genes may be present in the cassette thus conferring multiple-resistance to other antibiotics on the organism (Ito et al. 2001). Apart from the inability of an antibiotic to bind to the target site due to structural defect of such a site, other mechanisms that may also usually play significant roles in the development of resistance in bacteria such as MRSA include efflux phenomenon resulting in continuous pumping of antimicrobial drugs out of the bacterial cell. Others are alteration in the outer-membrane proteins which
limit the access of drugs to the cell; resistance can also occur from high level production of \( \beta \) lactamase (Hackbart et al. 1995). MRSA is produced when MSSA acquires a genetic element called SCC\( m \)ec. SCC is a basic mobile genetic element that serves as the vehicle for gene exchange among staphylococcal species; it has been documented in some coagulase-negative Staphylococci as well as in \( S. \ aureus \) (Luong et al. 2002).

### 2.1.6 Association of \( mecA \) gene in MRSA:

Most clinical isolates of Methicillin-Resistant \( Staphylococcus \ aureus \) have the \( mecA \) gene which encodes for the production of PBP2a, a modified Penicillin binding protein with low affinity for \( \beta \)-lactam antibiotics (Hiramatsu, K et al. 2001, Ito, T et al. 1998). \( MecA \) gene is enclosed in a \( Staphylococcal \) chromosomal cassette \( mec \) (SCCmec), which is around 21 to 60 kb. It is a mobile genetic element that may also contain genetic structures such as 554, PUB110, and PT181 which encode resistance to non-\( \beta \) lactam antibiotics (Gorak, E et al. 1999). The \( mecA \) gene codes for resistance to Methicillin and all other \( \beta \)-Lactam antibiotics in \( S. \ aureus \) (Grubb et al. 1999). The \( mecA \) gene is regulated by two genes, mec R1 and mec 1, located upstream of the \( mecA \) gene (Lencastre, H et al. 1994), and these regions together with \( mecA \) have been referred to as the \( mec \) complex (Shopsin, B et al. 2000). Four types of SCC \( mec \) have been described (Dufour, P et al. 2002).
2.1.7 Prevalence of Methicillin Resistant Staphylococcus aureus in India

*Staphylococcus aureus* continues to be a dangerous pathogen for both community-acquired as well as hospital-associated infections. Methicillin Resistant *S. aureus* (MRSA) is now endemic in India. The incidence of MRSA varies from 25 percent in Western India to 50 percent in Southern India (Anthony, L et al. 2002, Patel, A.K et al. 2010). Community acquired MRSA (CA-MRSA) has been reported increasingly in India (Gopalkrishnan,R et al. 2010).

The prevalence of MRSA in a study from Chennai was reported as 40-50% (Patel, A.K et al. 2010). Other studies have also shown a high MRSA prevalence in various parts of the country ranging from 40.6% to 59.3% (Fitzgerald, R.F et al. 2001, Muralidharan, S et al. 2009, and Anupurba, S et al. 2003). However, prevalence of 31.1% and 23.6% has also been reported (60, 61). Srinivasan S. et al. found that surgical units accounted for 80% of the MRSA isolated and postoperative infections in Orthopedics accounted for 28% (Mojumder, D et al. 2001). A study in Delhi showed prevalence of MRSA in blood culture to be as high as 35% in the wards and 43% in the ICUs (Srinivasan, S et al. 2006).

The prevalence of MRSA varies between regions and between hospitals in the same region as seen in a study from Delhi, where the MRSA prevalence in nosocomial SSTI (Skin and Soft tissue infections) varied from 7.5 to 41.3 percent between three tertiary care teaching hospitals (Wattal, C et al. 2010).

Other studies show that MRSA incidence was as low as 6.9 percent in 1988 and reached to 24 and 32.8 percent in Vellore and Lucknow, in 1994, respectively and was of the same order in Mumbai, Delhi and Bangalore in 1996 and in Rohtak and
Mangalore in 1999 (Geha, D.J et al. 1994). However, in some of the centers, it was as high as 80 percent. In India the isolation varied from 20-40 percent (Beck, W.D et al. 1986).

2.1.8 Epidemiology of Methicillin Resistant Staphylococcal aureus (MRSA):

Resistance to methicillin was uncommon until the late 1960s, when a multidrug-resistant MRSA (eg, phage type 83Acomplex) emerged in Europe (Jessen O et al.1969). For unknown reasons, the incidence of this MRSA in human infections gradually declined (Kayser F.H et al.1975) for nearly a decade following this decline, MRSA clones were infrequently encountered and limited primarily to major urban hospitals. However, a successful expansion of MRSA, which began in the late 1970s, turned into a nonstop evolutionary journey. MRSA resistant to gentamicin emerged in Europe and the United States (Kaene C.T et al. 1984) and a multidrug-resistant MRSA became epidemic in Australia. In the late 1980s MRSA rates in teaching hospitals reached 14% in Australia, while in the United States they increased from 8% to 22% by the end of the decade. At the same time, an epidemic clone (EMRSA), thought to have been imported from Australia, was propagating in the United Kingdom (Cookson B.D et al.1988) and soon all of Europe and the United States were seeing dramatic increases in MRSA infections. To illustrate this expansion, MRSA comprised nearly 60% of S. aureus organisms isolated in US intensive care units (ICUs) in 2003. Similarly in Latin America, rates of MRSA surpassed 50% in over half of the countries, and a similar situation was observed in many institutions from the Asia-Pacific region (Bell, J.M et al. 2002)
2.1.9 Community Acquired MRSA:

Definition: MRSA infections that are acquired by persons who have not been recently (within the past year) hospitalized nor had a medical procedure (such as dialysis, surgery, catheters) are known as community-acquired MRSA (CA-MRSA) infections, according to the Centers for Disease Control and Prevention (CDC). Community outbreaks have been reported in sports teams, child care attendees, prison inmates, and diverse populations where habitation is relatively concentrated (Klein E et al. 2007).

Methicillin-resistant Staphylococcus aureus (MRSA) is identified as a nosocomial pathogen throughout the world (Diekma et al. 1999). Community-Acquired MRSA was rarely reported (Levine, D.P et al. 1982). Recent studies suggest that the epidemiology of MRSA may be changing as the isolation of MRSA is no longer limited to hospitalized patients or persons with predisposing risk factor (Gregory J. Moran et al. 2005, Stryjewski et al. 2008). However, the prevalence of MRSA colonization in healthy persons in the community has been shown to be low, even though MRSA is highly endemic in hospital settings (Gillet, Y et al. 2002).

A unique clone of MRSA acquired in the community was first described in Western Australia (Udo, E.E et al. 1993). After few years, other community-acquired MRSA clones were recognized in Europe (CDC. 1999), the United States (Chambers, H.F et al. 2001), Latin America (Swenson, J.M et al. 2007) and Asia (Felton, A et al. 2002). These clones often affected young people without contact with healthcare producing purulent skin infection (Swenson, J.M et al. 2005) or pneumonia (Swenson, J.M et al. 2007). MRSA is also emerging in communities, particularly in the United States, where 28% of Community-acquired S. aureus strains may be resistant to Methicillin (CLSI 2006, Anand, K.B et al. 2009). The prevalence of MRSA in the
community is predicted to increase substantially due to the dissemination of a successful SCCmec type by horizontal transfer (Anand, K.B et al. 2009, Iwakanea, K et al. 2002).

2.1.10 Hospital - Acquired MRSA:

Definition: The CDC defines hospital-acquired MRSA (HA-MRSA) in persons who have had frequent or recent contact with hospitals or healthcare facilities (such as nursing homes or dialysis centers) within the previous year, have recently undergone an invasive medical procedure, or are immune compromised (Klein E et al. 2007).

Although HA-MRSA and CA-MRSA have distinct clinical differences, both are transmitted in the same fashion—most frequently through direct skin-to-skin contact or contact with shared items or surfaces (such as towels or bandages) that have come into contact with someone else’s colonized or infected skin. Currently, MRSA originates more frequently outside of the hospital, implying it is brought into the hospital upon admission as either the CA-MRSA or HA-MRSA genotype.

A study by Mahamat et al. (2007) set out to determine the most effective methods of preventing the spread of MRSA in hospitals. The study used a control hospital (which received a new antibiotic treatment policy as well as an alcohol hand gel policy) and an intervention hospital (which received the antibiotic treatment policy, alcohol hand gel policy as well as environmental screening, chlorine disinfection and admission screening) to determine the relative effectiveness of these policies. The new antibiotic treatment policies did not prove to be an effective way of fighting the spread of MRSA infections in hospitals. The introduction of alcohol hand gel for improved hand hygiene did however prove to be very effective in reducing the spread of MRSA. In the control hospital (alcohol hand gel introduced after new antibiotic treatment policy) there was a 30% decrease in the spread of MRSA in the hospital. In
the intervention hospital the introduction of alcohol hand gel reduced the spread of MRSA by 21% (Mahamat et al. 2007).

2.1.11 Detection of Methicillin Resistant *Staphylococcus aureus*:

MRSA strains that possess *mecA* gene are either heterogeneous or homogenous in their expression of resistance. The heterogeneous expression occasionally results in low minimal inhibitory concentrations and consequently the isolates may be interpreted as susceptible (Sakoulas, G et al. 2001). In the recent past, there have been multiple reports on the use of Cefoxitin as a surrogate marker for detection of *mecA*-gene-mediated Methicillin Resistance (Prasad, K.N et al. 2000, Ammon, H.P et al. 1991). Cefoxitin is a potent inducer of the *mecA* regulatory system (Lampe, V et al. 1913).

The Clinical and Laboratory Standards Institute (CLSI) guidelines have recommended Cefoxitin Disc Diffusion method for the detection of MRSA. This is performed by using a 30mg Cefoxitin disc. An inhibition zone diameter of ≤19mm is reported as Methicillin Resistant and ≥20mm is considered as Methicillin Sensitive (Shishodia, S et al. 2005). The conventional methods to detect MRSA in the laboratory include Oxacillin Screen Agar, disk diffusion using Cefoxitin, Oxacillin disc, Oxacillin MIC by agar or broth dilution methods (Kotwal, G.J et al. 2005). Polymerase Chain Reaction is considered the gold standard (Sarka et al. 2007, Cheng, AL et al. 2001).

2.1.12 Resistance to higher Antibiotics and New Drugs:

With the emergence of Resistance to the Penicillinase Resistant Penicillin, the Glycopeptide agent Vancomycin became the treatment of choice, for infections due to MRSA. Vancomycin received approval by the US Food and Drug Administration in 1958 (Rotun, S.S et al. 1999). However in May 1996, the first documented infection
caused by *S. aureus* strain with intermediated resistance to Vancomycin was reported from Japan (Mohr, J.F et al. 2007, CDC, 1997). Subsequently *S. aureus* strains with low level resistance to Vancomycin were recovered from patients seen in Michigan, New York State, New Jersey and Illinois (Hiramatsu, K et al. 1997, Rotun, S.S et al. 1999, CDC, 1999).

### 2.1.13 Methicillin Resistant *Staphylococcus aureus* Disease Burden:

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare and community associated infections worldwide. The European Centre for Disease Prevention and Control (ECDC) has calculated that Health-care-Associated Infections (HAIs) involve 4.1 million patients annually in the European Union (EU) member states and that such infections directly result in approximately 37,000 Deaths (Gadepalli, R et al.2009). The main cause of concern is the continuous emergence of various multidrug-resistant bacteria in many healthcare institutions, which narrows the spectrum of effective antibiotics to a clinically challenging extent (Gadepalli, R et al. 2009).

Among the multi-drug resistant bacteria, Methicillin-Resistant *Staphylococcus aureus* (MRSA) is a major cause of Health-care Associated Infections (HAIs) in the EU. Overall MRSA accounts for 44% of these Health-care-Associated Infections, 22% of attributable extra deaths and 41% of extra days of hospitalization associated to the infection. In the pre-antibiotic era, blood stream infections due to *S.aureus* yielded more than 80% mortality (Skinner, D et al. 1941). Contemporary studies have shown that in hospitals mortality rates for patients with blood stream infections due to MRSA are in the range of 30% but can be as high as 65% in some centers (ECDC. 2007, Whitby ,M et al. 2001).
A study by the Centre for Disease Control and Prevention from 1999 to 2000 estimated annual hospitalization of 125,969 for the diagnosis of MRSA infections in the United States, including 31,440 for blood stream infections and 29,823 for pneumonia (LeKraker Me et al. 2011). More recent estimates in the US indicate that MRSA causes approximately 95,000 invasive infections and 19,000 deaths per year (Kuehnert, M.J et al. 2005). Thus, the amount of mortality is higher than that produced by Human Immuno-deficiency virus, hepatitis virus, tuberculosis and influenza combined (Kelevens, R.M et al. 2007).

2.2.1 Gram negative bacteria and infections:

The gram-negative bacilli vary in the frequencies that they cause the 4 most frequent types of hospital-acquired infection: pneumonia, surgical site infection (SSI), urinary tract infection (UTI), and bloodstream infection (BSI) (Weinstein R.A. 1991). During the past 20 years, changes in health care, infection-control practices, and antimicrobial use and resistance may have influenced the frequency that these gram-negative organisms are associated with hospital-acquired infection. Gram-negative bacilli such as Enterobacteriaceae and Pseudomonas aeruginosa are the leading causes of nosocomial blood stream infections. Antibiotic-resistant strains have emerged among the gram-negative bacilli and are being increasingly recognized (Itokazu et al. 1996). This marked increase in the incidence of infections due to antibiotic-resistant gram-negative bacilli in recent years is of great concern. It is presumed that infections caused by antibiotic-resistant bacteria result in greater mortality, longer hospitalization, and higher costs than infections caused by antibiotic-susceptible bacteria, although little data are available to support this intuitive concept (Blot et al. 2002). The assumption that infections caused by antibiotic-resistant
bacteria are associated with a higher mortality rate is based on the possibility that appropriate antimicrobial therapy for such infections might be initiated later than for infections caused by antibiotic-susceptible bacteria. Appropriate antimicrobial therapy has been shown to reduce mortality among patients with gram-negative bacteremia (Kang et al. 2003) and, when initiated early, to have a favourable effect on outcome in critically ill patients with bacteremia or other serious infections.

2.2.2 Drug resistance in Gram - Negative Bacteria: Enterobacteriaceae

The emergence and spread of resistance in Enterobacteriaceae are complicating the treatment of serious nosocomial infections and threatening to create species resistant to all currently available agents. Approximately 20% of Klebsiella pneumoniae infections and 31% of Enterobacter spp infections in intensive care units in the United States now involve strains not susceptible to third-generation cephalosporins. Such resistance in K pneumoniae to third-generation cephalosporins is typically caused by the acquisition of plasmids containing genes that encode for extended-spectrum β-lactamases (ESBLs), and these plasmids often carry other resistance genes as well. ESBL-producing K pneumoniae and Escherichia coli are now relatively common in healthcare settings and often exhibit multidrug resistance. ESBL-producing Enterobacteriaceae have now emerged in the community as well. Salmonella and other Enterobacteriaceae that cause gastroenteritis may also be ESBL producers, which is of relevance when children require treatment for invasive infections. Resistance of Enterobacter spp to third-generation cephalosporins is most typically caused by overproduction of AmpC β-lactamases, and treatment with third-generation cephalosporins may select for AmpC-overproducing mutants.
Some *Enterobacter cloacae* strains are now ESBL and AmpC producers, conferring resistance to both third- and fourth-generation cephalosporins. Quinolone resistance in Enterobacteriaceae is usually the result of chromosomal mutations leading to alterations in target enzymes or drug accumulation. More recently, however, plasmid-mediated quinolone resistance has been reported in *K pneumoniae* and *E coli*, associated with acquisition of the *qnr* gene. The vast majority of Enterobacteriaceae, including ESBL producers, remain susceptible to carbapenems, and these agents are considered preferred empiric therapy for serious Enterobacteriaceae infections. Carbapenem resistance, although rare, appears to be increasing. Particularly troublesome is the emergence of KPC-type carbapenemases in New York City. Better antibiotic stewardship and infection control are needed to prevent further spread of ESBLs and other forms of resistance in Enterobacteriaceae throughout the world (David L. 2006).

### 2.3.1 Turmeric and their taxonomical classification:

Turmeric (the common name for *Curcuma longa*) is an Indian spice derived from the Rhizomes of a plant and has a history of use in Ayurvedic Medicine as a treatment for inflammatory conditions. *C.longa* is a perennial member of the *Zingiberaceas* family and is cultivated in India and other parts of Southeast Asia (Nita Chainani et al. 2003). The primary active constituent of turmeric and the one responsible for its vibrant yellow colour is curcumin first identified in 1910 by Lampe and Milobedzka (Kloss, W.E et al. 1999).

*Curcumin* is a yellow-orange pigment and the most-important ingredient in turmeric. Curcumin has many clinical applications particularly as a powerful, yet safe, anti-inflammatory agent.
Turmeric was described as C. longa by Linnaeus and its taxonomic position is as follows:

- **Class**: Liliopsida
- **Subclass**: Commelinids
- **Order**: Zingiberales
- **Family**: Zingiberaceae
- **Genus**: Curcuma
- **Species**: longa

The wild turmeric is called *C. aromatica* and the domestic species is called *C. longa*.

### 2.3.2 History of turmeric:

Marco polo (1280 AD) refers to turmeric as Indian saffron used for dyeing cloths. As far as documented evidence, it has been used daily in India for at least 6000 years as medicine, beauty aids, cooking spice and a dye. Ostensibly it was used to worship the Sun during the solar period of India, a time when Lord Ram Chandra walked the Earth. It was mentioned in the holy text “Atharveda” of India. Buddhist monks have used turmeric as a dye for their robes for at least 2000 years. It was listed in an Assyrian herbal circa 600 BC and was mentioned by Discorides in the herbal, which was the western herbal rediscovered 700 years ago by Marco Polo and it is used in traditional treatment against lethal poison of pit vipers in China. This was mentioned in the Pent-Sao of the 7th century. For at least 1000 years Chinese have used turmeric as a medicine especially for the spleen, stomach and liver medicines. They use it to stimulate and purify and as an anti-biotic, anti-viral and an analgesic. As such it is used to stimulate, strengthen the blood, decrease blood pressure, to clean abdominal pain and stagnation in men, woman and children. They consider it one of
the better herbals for woman because it stimulates the uterus and clears menstrual stagnation. In the 1870’s, chemists discovered turmeric orange yellow root powder turned reddish brown when exposed to alkaline chemicals. This discovery led to the development of turmeric paper to test for alkalinity. European and American herbalists up until the early 20th century had little interest in turmeric. In one western herbal from the early 20th century, Maude Greve’s book A Modern Herbal, in which she gives a botanical description and the constituents of the herb as if the herb was of some importance, but then under medicinal actions and uses she says; “Turmeric is a wild aromatic stimulant seldom used in medicine except as a colouring. It was once a cure for jaundice. Its chief use is in the manufacture except as a colouring. It was once a cure for jaundice. Its chief use is in the manufacture of curry powder. It is used as an adulteration of mustard and a substitute for it and forms once of the ingredients of cattle condiments. Turmeric paper is used as a test for alkaloids and boronic acid”. Daniel B. Mowrey states that, “Serious research on turmeric began in Germany, in the early 1920’s. Sesquiterpenes in the essential oil of turmeric were isolated in 1926 and to them was ascribed the therapeutic activity (Jaggi Lal et al 2012).

2.3.3 Indian Scenario for the Cultivation of Turmeric:

India is the largest consumer, producer and exporter of turmeric in the world. The country consumes most (80 percent) of its turmeric production and it exports the surplus. Turmeric is grown in as many as 25 states in India with Andhra Pradesh, Tamilnadu, Karnataka and Odisha being the leading producers. Other main producers of turmeric are Gujarat, West Bengal, Assam, Meghalaya and Maharashtra. India has nearly 1.73 lakh hectares under turmeric cultivation with a total production of 8.55 lakh tonnes during the year. Andhra Pradesh, topped both in area and production during the year 2005-2006, with 69,990 hectare (40.46%) and 518550 tonnes.
(60.60%), respectively. Tamilnadu followed with acreage of 25,970 hectares (15.01%) and production of 1, 43,358 tonnes (16.75%) (Jaggi Lal et al. 2012).

2.3.4 Chemical composition of turmeric:

Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The essential oil (5.8%) obtained by steam distillation of rhizomes has α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) (Kappor, L.D et al. 1999). Curcumin (diferuloylmethane) (3–4%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%) (Ruby et al. 1995). (Fig 4) Demethoxy and bisdemethoxy derivatives of curcumin have also been isolated (Vopel et al. 1990). Curcumin was first isolated in 1815 and its chemical structure was determined by Roughley and Whiting (Roughley, P et al. 1973) in 1973. It has a melting point at 176–177°C; forms a reddish-brown salt with alkali and is soluble in ethanol, alkali, ketone, acetic acid and chloroform.
Fig. 4 Structure of Curcumin
2.3.5 Biological activity of turmeric and its compounds:

Turmeric powder, Curcumin and its derivatives and many other extracts from the rhizomes were found to be bioactive. The structures of some of these compounds (Araujo et al. 2001) are presented in Fig 4. Turmeric powder has healing effect on both aseptic and septic wounds in rats and rabbits (Gujral et al. 1953). It also shows adjuvant chemo protection in experimental fore stomach and oral cancer models of Swiss mice and Syrian golden hamsters (Azuine, M et al. 1994). Curcumin also increases mucin secretion in rabbits (Lee et al. 2003). Curcumin, the ethanol extract of the rhizomes, sodium curcuminate, [feruloyl-(4-hydroxycinnamoyl)-methane] (FHM) and [bis-(4-hydroxycinnamoyl)-methane] (BHM) and their derivatives, have high anti-inflammatory activity against carrageenin-induced rat paw oedema (Ghatak, N et al. 1972) (Srihari Rao et al. 1982). Curcumin is also effective in formalin induced arthritis (Ghatak, N et al. 1972). Curcumin reduces intestinal gas formation (Bhavani Shankar et al. 1979) and carbon tetrachloride and D-galactosamine induced glutamate oxaloacetate transaminase and glutamate pyruvate transaminase levels (Kiso, Y et al. 1983) (Hikino, H et al. 1985). It also increases bile secretion in anaesthetized dogs (Ramprasad, C et al. 1956) and rats (Jentzsch, K et al. 1959) and elevates the activity of pancreatic lipase, amylase, trypsin and chymotrypsin (Platel, K et al. 2000). Curcumin protects isoproterenol-induced myocardial infarction in rats (Nirmala, C et al. 1996). Curcumin, FHM and BHM also have anticoagulant activity (Kosuge, T et al. 1985) (Srivastava, R et al. 1985). Curcumin and an ether extract of C. longa have hypolipemic action in rats (Rao, S et al. 1970), lower cholesterol, fatty acids and triglycerides in alcohol induced toxicity (Rukkumani, R et al. 2003). Curcumin is also reported to have antibacterial (Bhavani Shankar et al. 1979), antiamoebic (Dhar, M. L

2.3.6 Safety of Curcumin, a Component of Turmeric:

Turmeric has been used for its medicinal properties for various indications and through different routes of administration- topically, orally and by inhalation. Curcuminoids are compounds of turmeric, which include mainly curcumin (diferuloylmethane) demethoxycurcumin, and bisdemethoxycurcumin (Lowy, F.D et al. 1998). Safety evaluation studies show curcumin is well tolerated at very high doses without any adverse effects. For centuries, curcumin has been consumed as a dietary spice at
doses up to 100mg per day. Recent human clinical trials found no toxicity and no adverse side effects in curcumin when administered at doses of 8,000 mg per day for three months (Maranan, M.C et al. 1997). Another study shows that curcumin has been demonstrated to be safe in six human trials (Wootton et al. 2001).