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Curcumin – Extraction, Synthesis and Application in Modern Drug Research: A Mini Review

Sujata Sengupta[1] , Sharda Mahilkar Sonkar[1], Anand Sonkar[2*],Romila Rawat Bisht[2],

Richeek Debnath[3], Khyati Kinger[1], Dinesh Kumar Gautam[4]

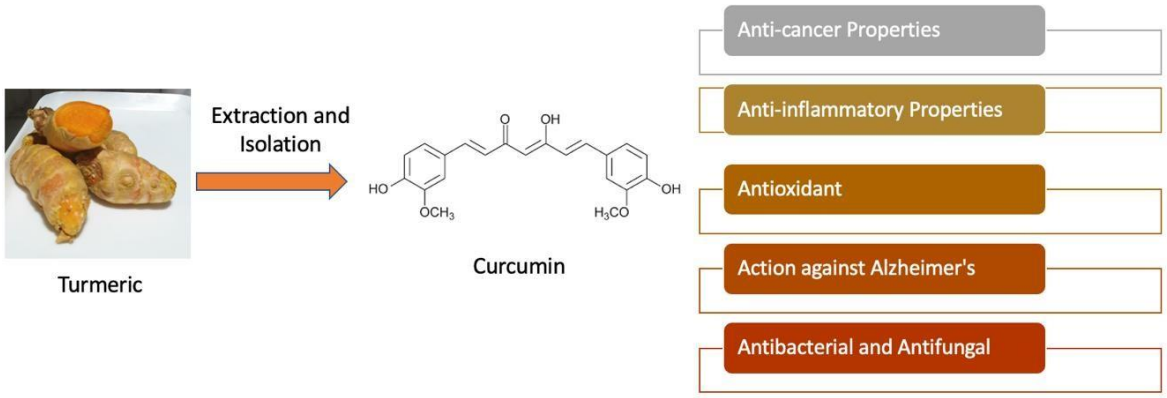
[1]Department of Chemistry, Miranda House, University of Delhi, Delhi 110007

[2]Department of Botany, Hansraj College, University of Delhi, Delhi 110007

[3]Indian Institute of Science Education and Research (IISER) Berhampur, Ganjam-760003, Orissa, India

[4]Department of Zoology, Hansraj College, University of Delhi, Delhi 110007

*Corresponding author: asonkar@hrc.du.ac.in



ABSTRACT: -

The rhizome of the *Curcuma longa* is known to contain curcumin, demethoxycurcumin, and bisdemethoxycurcumin, three naturally occurring yellow pigments belonging to the curcuminoid family. Curcuminoids and all its derivatives are active components in many nutraceuticals and cosmetic products. The therapeutic benefits of curcumin are exhaustive and have been proven by numerous scientific investigations. This mini review aims to delve

into the various methods of extraction and isolation of curcumin along with its synthetic route. In addition, the various biological activities, like the antioxidant and antibacterial characteristics, of curcumin are also discussed.

Keywords:- Curcumin, extraction, synthesis, antioxidant

INTRODUCTION: -

Curcumin (diferuloylmethane), a low-molecular weight member of the curcuminoid class of compounds, is a bright yellow chemical produced by plants of the *Curcuma longa* species (Priyadarshani 2014). It is the principal curcuminoid found in turmeric, a yellow Indian spice and member of the ginger family, *Zingiberaceae*. Turmeric is best known as a natural ingredient common to Indian and Asian cooking. In addition, turmeric is used as a preservative, provides an aesthetic appeal, increases shelf life and the nutritive value of foods (Eigner et al. 1999). Furthermore, turmeric has a long history of use in Ayurveda, often used for the treatment of anti-inflammation, joint pain, dysentery, and chest congestion. In the West, turmeric is approved by the US FDA as a food additive and is used in nutraceuticals, beverages and processed foods. It also finds use as a natural coloring agent and a common ingredient in pharmaceuticals, hair dyes and other cosmetics compounds (Grant et al. 2000).The importance of turmeric as a therapeutically useful substance was supported with the discovery and isolation phenolic class of compounds known as curcuminoids. These compounds are now known to be strong antioxidants. Three primary curcuminoids- curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Figure 2), of which curcumin is the most predominant, are among the major bioactive ingredients present in turmeric. The yellow pigment curcumin or diferuloylmethane accounts for nearly 60% to 70% of crude turmeric extracts. Of the various curcuminoids, it is curcumin, which is attributed to the

therapeutic values of turmeric, and is now commonly sold as an herbal supplement, cosmetics ingredient, food flavoring and coloring agent (Nelson et al. 2014, Keith 2020, Priyadarshani 2014).

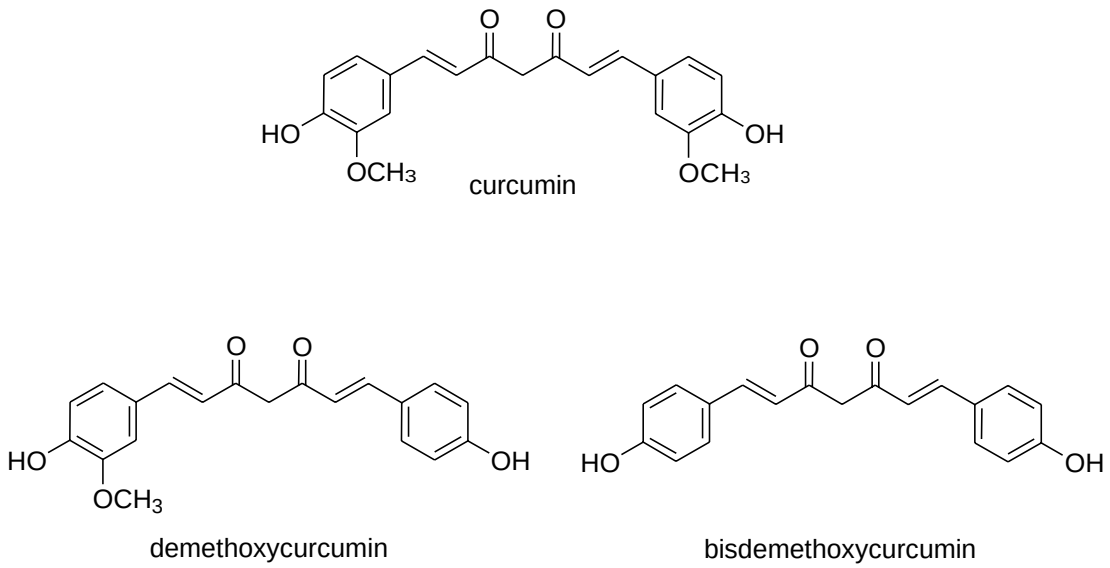


Figure 1 : Structure of the 3 major curcuminoids in turmeric

There are more than 100 species in the Curcuma family and a characteristic of these species is the yellow orange hue. The substances responsible for this tint are curcuminoids – a class of polyphenols. The three major chemical constituents and biological activities of turmeric are accounted for by approximately 77% curcumin (CUR), 17% demethoxycurcumin (DMC),and 3% bisdemethoxycurcumin (BDMC).(Amalraj et al. 2017) Chemically, curcumin, is a diarylheptanoid phenolic pigment with molecular formula $C_{21}H_{20}O_6$, is a solid at room temperature and has a molecular weight of 368.38 g/mol. Its IUPAC nomenclature is 1,7-bis (4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione. It is a hydrophobic molecule readily soluble in hydrocarbon solvents and is almost entirely insoluble in water. Curcumin ishighly reactive, particularly due to its extended conjugation of double bonds and is known to be a strong oxidizing agent (Grynkiewicz et al. 2012). Both, DMC and BDMC are naturally

occurring bioactive analogues of curcumin. Demethoxycurcumin is a polyphenol beta-diketone, where one of the methoxy groups in curcumin is replaced by a hydrogen. It is one of the major bioactive components in many curcumas, especially Curcuma amada and Curcuma aeruginosa, and is known to play a key role as a metabolite and anti-inflammatory agent. Bisdemethoxycurcumin lacks two methoxy groups on the aromatic rings of curcumin and is used as a pigment and nutraceutical with antimutagenic properties (Francisco et al. 2002). All three of the curcuminoids found in Curcuma longa have been shown to have anti- oxidant properties.

Recently, curcumin has received a greater interest in biological and pharmaceutical industry (Grynkiewicz et al. 2012). Curcumin, the most abundant diarylheptanoid, is known to treat many diseases, including cancer (Aggarwal et al. 2003, Batra et al. 2019, Willenbacher et al. 2019), diabetes (Pivari et al. 2019), inflammation and even neurodegenerative diseases such as dementia and Alzheimer's (Ghosh et al. 2015). It is recognized as a molecule that can treat a range of illnesses by modifying growth factors, kinases, transcriptional regulators, inflammatory cytokines, pro- and anti-apoptotic proteins, and enzymes. Specifically, during the inflammatory stage of wound healing, curcumin inhibits cytokines. Curcumin reduces inflammation by acting through a variety of pathways. It activates immune mediators and possesses antioxidant qualities. Curcumin in its anticancer capacity is known to reduce transcription factor activity and inhibit the proliferation of a number of tumor cells (Rathore et al. 2020, Giordano et al. 2019, Esatbeyoglu et al. 2012). However, despite all its potential benefits, the clinical applications of curcumin are quite limited primarily due to its low oral bioavailability, poor solubility in water and its instability in acidic pH (Huang et al. 2020). Curcumin has limited bioavailability since an oral dose result in lower absorption, the molecule is quickly broken down by aldo-keto reductase in the gut and the liver and quickly removed from the body. In addition to having anti-inflammatory properties, curcuminoids

activate the body's natural antioxidant defense mechanisms. Various reports indicate curcumin to have a strong ability for scavenging superoxide radicals, hydrogen peroxide and nitric oxide (NO) from activated macrophages and inhibit lipid peroxidation (Tilak et al. 2004).

ISOLATION OF CURCUMIN:-

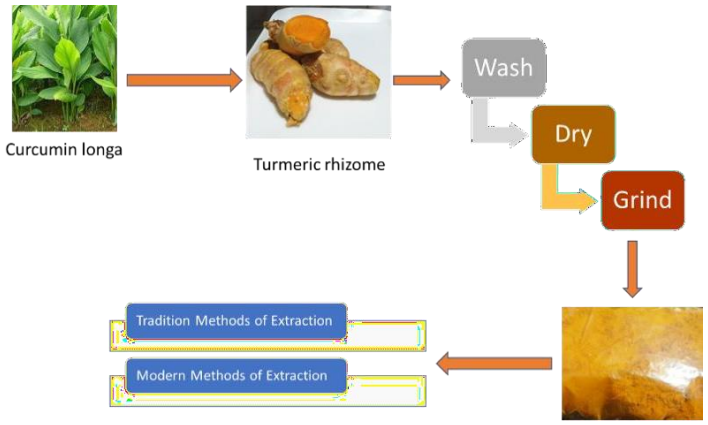


Figure 2: Steps of isolation of curcumin from turmeric

Isolation of natural bioactive compounds generally involve a series of steps – selection of the plant component, cleaning and subsequent drying followed by extraction and purification of the desired compound (Tripathy et al. 2021, Chávez-González et al. 2020). The various extraction methods available are generally categorized as traditional methods, such as Soxhlet extraction and modern techniques, involving ultrasound assisted extraction, microwave-assisted extraction, super critical fluid extractions and even with ionic liquids (Gökdemir et al. 2020). Traditional methods of isolation remain the extraction process of choice, primarily due to its simple methodology and low operating costs. Post isolation, the bioactive compounds are identified using various chromatographic techniques, such as thin-layer

chromatography (TLC) and high-performance liquid chromatography (HPLC) (Degot et al. 2020).

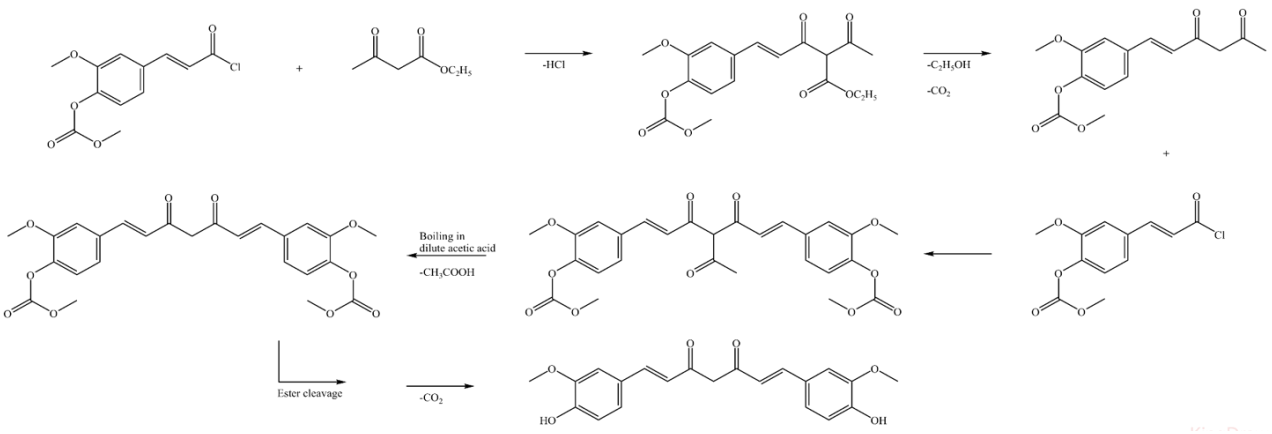
Curcumin is extracted from the rhizome of the turmeric plant. Generally, it is the powdered sample of turmeric which provides the highest extraction yield. In a typical procedure, hexane and acetone are used to extract the curcumin in the powder form. The acetone extract is dried and concentrated to isolate curcumin. Furthermore, Yulianto et al. had demonstrated that the highest concentration of curcumin is extracted at high temperatures with a low solid: liquid ratio (1:10) (Yulianto et al. 2019).The choice of a suitable solvent also plays a critical role in the extraction process. Extraction with ethanol at 35 ^{o}C generally provides the highest curcumin extraction yield (72%) compared to solvents such as acetone, methanol, and ethyl acetate (Shirsath et al. 2017).Various modern methods of extraction of curcumin have now been explored. Subcritical solvent extraction of curcumin using water/ethanol mixture (50:50 v/v) at high temperatures provided an extraction yield of almost 14%.[27] Zhou and researchers have reported an optimized microwave assisted extraction of curcumin and other curcuminoids from Curcuma longa in 55 seconds using 69% ethanol in a 21:1 liquid: solid ratio. In addition, enzyme-assisted ionic liquid extraction and surfactant free microemulsion extraction techniques have also been optimized for the extraction of curcumin (Zhou et al. 2015, Sahne et al. 2017).

Post extraction, curcumin is isolated by a variety of analytical techniques (Frank et al. 1971). Mohan and co-workers have reported a simple procedure for the isolation of curcumin which may be performed in the laboratory as part of undergraduate curriculum (Anderson et al. 2000). The procedure exposes chemistry students to common laboratory techniques of trituration, recrystallization, column chromatography and preparative thin layer chromatography. According to the procedure, isolation of curcumin using column

chromatography first involves the trituration of the crude extracted sample with hexane followed by dissolving in minimum amount of dichloromethane-methanol solvent ratio (99:1 v/v) and loading onto a column packed silica gel. Elution of the column was done with the same solvent. TLC analysis of the various fractions show the presence of all three major components of turmeric, of which the least polar colored component was determined to be curcumin (M. Pt. 178-182 ^{o}C and confirmed by ^{1}H-NMR and ^{13}C-NMR). Curcumin and its derivatives may also be isolated from preparative thin-layer chromatography in the undergraduate setting. According to procedure, approximately two hundred milligrams of the crude solid obtained after trituration with hexanes is dissolved in 1mL of dichloromethane - methanol (99:1 v/v) and loaded on a preparative TLC plate. The plate is developed at which the uppermost colored band had an R_f value of 0.52. The silica gel from this band is scraped off and dried for 5 min with 25 mL of dichloromethane-methanol (99:1 v/v) solution. Filtration followed by removal of the solvent typically gives 60 mg of curcumin.

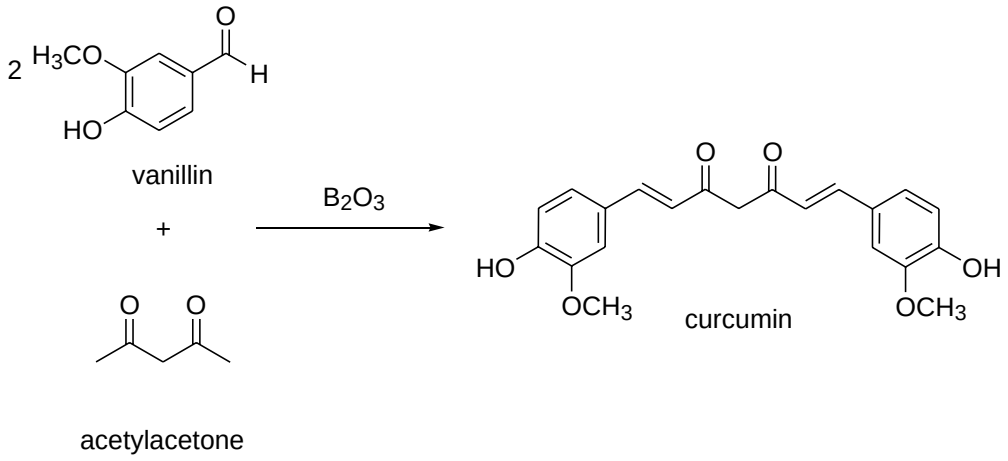
SYNTHESIS OF CURCUMIN:-

In 1918, Lampe synthesized curcumin in five steps starting from ethyl acetoacetate and carbomethoxy feruloyl chloride (Scheme 1) (Lampe et al. 1913). Simple condensation followed by saponification and decarboxylation leads to an intermediate product which was again reacted with carbomethoxy feruloyl chloride. The resulting condensation product, a carbomethoxy di feruloyl acetone derivative, was then cleaved under hot acidic conditions. Curcumin was finally obtained after a final saponification and decarboxylation.



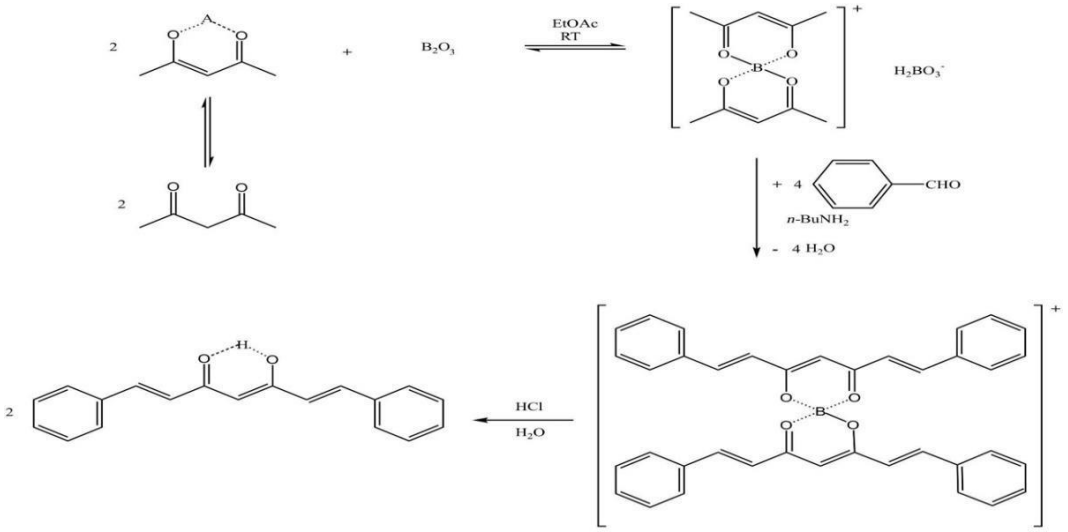
Scheme 1: Synthesis of curcumin according to Lampe

In 1950, Pavolini synthesized curcumin in a one-step reaction by condensing 2 parts of vanillin and 1 part of acetylacetone in the presence of boron trioxide. However, the yield of curcumin obtained was only about 10% (Scheme 2) (Pabon 1964).



Scheme 2: Synthesis of curcumin according to Pavolini[33]

In 1964, Pabon improved upon the Pavolini synthesis by reacting acetylacetone and substituted aromatic aldehydes using boron trioxide, trialkyl borates and n-butylamine. Curcumin was prepared in nearly 80% yield using vanillin and acetylacetone/B_2O_3 in the presence of tri-sec. butyl borate and n-butylamine. The reaction was carried out in ethyl acetate at room temperature. In addition, eight structural analogues of curcumin were synthesized using the above protocol. Compounds related to curcumin have also been synthesized (Pabon 1964).



Scheme 3: Synthesis of curcuminoids according to Pabon

PHARMACOLOGICAL ACTIVITY OF CURCUMIN:-

For thousands of years, turmeric has been utilized as a plant-based medicine. In traditional Indian (Ayurveda) and Chinese medicine, turmeric is routinely prescribed for the treatment of inflammation (Yuvapriya et al. 2015). Curcumin has been linked to several positive health effects, including antioxidant, antibacterial, anti-inflammatory, analgesic, wound healing, and

eupeptic qualities. Recently, the health benefits of various natural and synthetic curcuminoids have been linked to neuroprotection, chemo- and cancer prevention (Eastbeyoglu et al. 2012). It is possible for curcumin to reduce both acute and chronic inflammation. In addition, as mentioned earlier, curcumin induces endogenour antioxidant defense mechanism and thus have anti-inflammatory properties.

Anti-inflammatory Action of Curcumin: Studies have shown curcumin to modulate several inflammatory mediators both in vitro and in vivo, by targeting cytokines, lipid mediators and proteolytic enzymes (Joe et al. 2004). Lokesh and co-workers have reported curcumin to inhibit the cellular uptake of arachidonic acid (AA). Arachidonic acid is readily oxygenated and transformed into various mediators, eicosanoids, which are known to modulate inflammatory reactions. (Joe B et al. 1999) In addition, curcumin is found to inhibit several phospholipases, including cyclooxygenases (COX), lipoxygenases (LO), all of which are involved in the release of arachidonic acid (Skrzypczak-Jankun et al. 2000). Furthermore, animal model studies on acute and chronic inflammation have clearly demonstrated curcuminto be as effect as reference drug phenylbutazone for acute inflammation.

Antibacterial and Antifungal Action of Curcumin: Traditional Indian and Chinese medicine have always used turmeric paste as an antibacterial agent for the treatment of small cuts and wounds. Recent studies by Mishra and coworkers have revealed curcumin and its various synthetic bioconjugates to be as effective as Cefepime and fluconazole, popular antibacterial and antifungal drugs respectively. In fact, these synthesized bioconjugates were found to be far more potent that curcumin itself, probably due to its improved cellular uptake and reduced metabolism in the body. These results indicate the strong potential of the

curcumin bioconjugates to be promising antibacterial and antifungal drugs (Mishra et al. 2005).

Anticancer Action of Curcumin: A random PubMed search on curcumin and cancer results in nearly 2000 articles till date, with numbers increasing yearly (Adams et al. 2005, Manson MM et al. 2005, Karunagaran et al. 2005). Numerous investigations have reported the anticarcinogenic activity of curcumin and its analogues against breast (Bachmeier et al. 2008), ovarian (Lin et al. 2007), gastric (Yu et al. 2011), colon (Milacic et al. 2008), lung (Yang et al. 2012), pancreatic (Kanai et al. 2014), prostate (Li et al. 2007) cancers and even leukemia (Tomit et al. 2006). Though the exact mode of action of curcumin in cancer prevention is yet to be clearly understood, studies suggest it may be due to its ability to induce apoptosis and arrest cell cycle. Furthermore, oxidative, and inflammatory tissue damage is known to play a key role in cancer progression. Therefore, due to its already known anti-inflammatory and anti-oxidant nature, curcumin offers a key role in suppressing tumor promotion and thereby prevent cancer. Curcumin is not only known to possesses anticancer ability alone but is known to improve the anticancer effects of several well-known anticancer drugs (5-fluorouracil, cis-platinum, paclitaxel and oxaliplatin and is known to modulate a diverse range of molecular targets in preclinical studies (Kanai M. et al. 2014). The promising preclinical results of curcumin's anticancer ability has attracted researchers in their quest to develop curcuminoids as promising chemo-preventive and chemotherapeutic drugs (Agrawal et al. 2010, Radhakrishna et al. 2004). Furthermore, in comparison to most cytotoxic anticancer drugs, curcumin has minimal toxicity- thus avoiding side effects such as vomiting, nausea and fatigue. As mentioned earlier, curcumin has been approved by the US FDA and the World Health Organization as a safe, non-toxic compound.

Action of Curcumin on Alzheimer's: Alzheimer's dementia (AD) is a multifactorial neurodegenerative illness that involves substantial neuronal loss. AD is often associated with chronic inflammation, excitotoxicity, oxidative damage, and mitochondrial dysfunction. Because of its potential anti-oxidative, anti-inflammatory, and anti-excitotoxic effects, curcumin was tested a promising therapeutic agent in the treatment of AD (Baum et al. 2004, Calabrese et al. 2003).

COMMERCIALLY AVAILABLE FORMULATIONS OF TURMERIC (CONTAINING CURCUMIN):-

There are several documented medical benefits of turmeric. Turmeric has been utilized in a variety of cosmetic treatments for millennia, as has been observed. Some ingredients in turmeric are claimed to help highlight a person's skin tone. It makes sense given the countless commercials for fairness creams that claim to include turmeric. The wonderful thing about turmeric is how affordable and effective it is. According to Indian custom, the bride gets covered in turmeric cream on the wedding day since it is thought that turmeric is excellent for skin. It even improves skin tone and eliminates acne and pimples. Many applications are reported for turmeric (Gopinath et al. 2018, Kaur et al. 2004, Kumar et al. 2013, Kole et al. 2005, Bhowmik et al. 2009).

Turmeric Oil: Turmeric powder is added to a natural oil. This turmeric-infused oil may then be rubbed on to the skin.

Turmeric Mask: Turmeric powder is mixed with cucumber or lemon juice to make a paste, applied on the skin for 15 minutes and rinsed off. Daily use has shown pigmentation to even out.

Turmeric Milk: Gives internal benefits to the body and has anti-inflammatory action.

Antioxidant Tea: Daily use of turmeric in tea detoxifies and reduces inflammation of the body.

CONCLUSION:-

The primary ingredient in the turmeric, a common condiment in Indian and South Asian cooking is the "golden" molecule curcumin. Extensive research now highlights the potential health benefits of curcumin and its related analogues and shows the pharmacological importance of these natural compounds. This review aims to highlight the various advances and advantages of curcumin in modern medicine and encourages the discovery of new synthetic analogues with best biological activities and minimal issues related to the bioavailability of curcumin.

DECLARATION:-

The manuscript has been prepared through contributions of all authors. All authors have given approval to the final version of the manuscript. All authors declare that they have no conflicts of interest.

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