Curcumin and its Derivatives: Review on Antimicrobial, Anti-Inflammatory and Antitumor Activity

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Abstract- *The rhizome of the Curcuma longa plant produces the bright yellow phytochemical known as curcumin. Since its initial extraction from this plant, curcumin has drawn significant interest from medical researchers. Among the many biological impacts of curcumin are anti-inflammatory, anti-microbial, anti-proliferative, antioxidant neuroprotective and anti-diabetic effects. Such adaptability is what Curcumin is a potential lead substance for the creation of new derivatives that could be used to manage a variety of conditions diseases including Alzheimer's, diabetes, and cancer. In this essay, the emphasis was on some of the animal species that are now available and clinical research that demonstrated the potential pharmacological effects.*

Keywords- curcumin, curcumin derivatives, anti-microbial, anti-inflammatory, cancer.

I. INTRODUCTION

Since the dawn of humankind, natural products have been widely used as a medicine for the management of a wide range of diseases that affected the human health. Natural product is a term which refers to any chemical substance that has been collected, extracted or isolated from living organism (1,2).

The development of new drugs from natural products is still representing a challenging task which necessitates a hard work. This task usually starts with the collection, extraction, isolation, purification and characterization of the natural product, and ends with the determination of its pharmacological and toxicological effect (3).

Despite all these difficulties, natural products still represent a significant source of compounds that have novelty in their chemical structures and modes of action Turmeric, the chief source of curcumin, is one of the most extensively studied plant and it has a well-defined history of applications in the ancient Indian(Ayurveda) and Chinese medicines for different therapeutic purposes. (4)

Curcumin is a bright yellow phytochemical which is derived from the rhizome of Curcuma longa of the ginger family (Zingiberaceae). In addition to curcumin, Curcuma longa contains two other curcuminoids; desmethoxycurcumin and bis-desmethoxycurcumin (5)

While it is freely soluble in organic solvents such as DMSO, ethanol, methanol, and acetone, curcumin has poor water solubility. Spectrophotometrically, it has a maximum absorption (λ_{max}) In methanol, it absorbs maximally at 430 nm, whereas in acetone, it absorbs maximally at 415 to 420 nm. (6)

Curcumin, also known as diferuloyl methane (Figure 1), is a spice. a molecule that is symmetric Its IUPAC designation is (1E, 6E) 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, and its molecular weight is 368.38 g/mole (7).

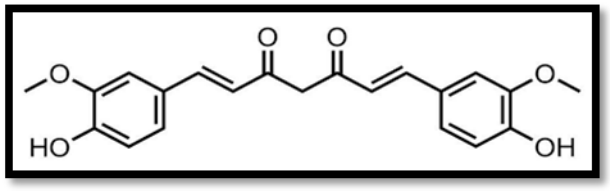

Figure1: chemical structure of curcumin

Since curcumin has been a staple of the human diet in several nations for hundreds of years, its safety profile has previously been established. It has also been utilized in for the treatment of several illnesses, including diabetes, Alzheimer's disease, cancer, and rheumatic disorders, by many people (8). According to reports, taking supplements containing curcumin may provide a number of health advantages, most of which are due to the compound's antioxidant and anti-inflammatory properties (9).

Although curcumin offers potential therapeutic effects through anti-inflammatory and antioxidant pathways, its low bioavailability which is brought on by poor water solubility, poor oral absorbability, and a quick metabolic rate limits the clinical uses of curcumin (10,11).

II. ANTIMICROBIAL ACTIVITIES

➢ ANTIBACTERIAL

Antibiotic resistance and treatment risk Failure represents a serious and growing global problem. In developing countries, infection with Staphylococcusaureus is a serious problem, especially in hospitals where methicill in resistant Staphylococcusaureus(MRSA) spread hard to control (12,13).

Over the years, the morbidity and mortality from MRSA infections is increased significantly. Scientists and researchers have had been evoked to study and find new compounds capable of solve this extremely serious problem (14).

Recently Accumulating data reveals that curcumin works potential antibacterial effects against both methicillin Staphylococcus aureus (MSSA) and MRSA. In addition to the extremely strong antibacterial ability when used Alone, curcumin also has a pronounced synergistic effect antibacterial activity against Staphylococcus aureus when simultaneously with different antibiotics such as ampicillin, ciprofloxacin, norfloxacin, gentamicin and amikacin (15,16).

Additionally, curcumin dramatically inhibits the development of extremely dangerous bacteria including Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis, Klebsiella pneumoniae and E. coli. For their antibacterial activity, many curcumin analogues have been synthesized and tested (17).

A new curcumin analogue known as CA2 (Figure 2) was created in recently published study by substituting two halogenated coumarin rings for the curcumin's guaiacol rings. With regard to common bacterial strains like Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia, and Hemophilus influenzae, the provided analogue displayed greater aqueous solubility and stronger antibacterial activity than curcumin (18).

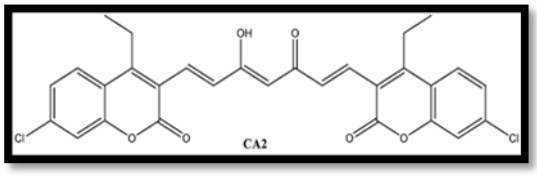

Figure:2 Curcumin analog with an antibacterial activity

III. ANTI-INFLAMMATORY ACTIVITY

Numerous diseases, including cancer, diabetes, cardiovascular disease, and neurodegenerative disorders, are largely caused by inflammation (19). NF- plays a significant role in the signal transduction pathways that are involved in inflammatory diseases, in addition to other media (20,21). As a result, it is believed that NF- represents a possible therapeutic target for many illnesses (22,23).

Numerous studies have confirmed that curcumin significantly suppresses NF-, which has an anti-inflammatory effect (24,25). Various inflammatory cytokines like TNF, IL-1, IL-6, IL-8, interferon, and certain other chemokines are downregulated by curcumin, according to previous research (26,27).

Paulino and colleagues created an analogue of curcumin called DM1 (Figure 3), which they tested for its impact on inflammatory mediators and found to have the to stop COX2 and iNOS from working (28.29).

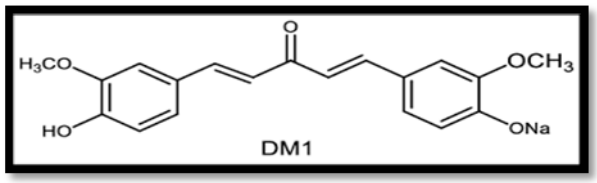

Figure:3 Curcumin analog with a potent anti-inflammatory effect

IV. ANTITUMOR ACTIVITY

The multistep process of carcinogenesis involves the upregulation of a great number of biochemical pathways and mediators. This upregulation includes growth and enzymes.cytokines, transcription factors, apoptosis inhibitors, proliferative enhancers, growth factor receptors, and cytokines.

A growing body of research suggests that curcumin can affect a wide range of carcinogens, including transcription factors, growth factors, and their receptors, which control apoptosis and cell proliferation. Additionally, benzo pyrene member curcumin has been shown to inhibit the mutagenic effects of tobacco smoke condensate (30,31).

Curcumin has the power to stop the growth of cancer cells and trigger apoptosis in a variety of cancer forms, including:

➢ BREAST CANCER

Breast cancer, which is thought to be the most frequent kind of malignancy in women, is mostly influenced

by oestrogen and its receptors, alpha and beta. Since oestrogen receptors are activated in a significant portion of breast cancer patients (around two-thirds), targeting these receptors is a crucial part of any plan for suppressing malignant tumours (32).

On research by Shao et al., it was established that curcumin's antiproliferative activities in oestrogen receptor-positive breast cancer cell lines are estro-dependent (33).
Additionally, this study shown that curcumin has a potent anti-invasive effect on the MCF-7 cell line, which lacks oestrogen. The downregulation of MMP-2 (matrix metalloproteinase) and the overexpression of TIMP-1 (tissue inhibitor of metalloproteinase), both of which are essential for the start and growth of tumour cell metastasis, appear to be the mediators of this activity (34).

By slowing the kinetics of microtubule assembly and triggering the mitotic checkpoint in MCF-7 cells, Calaf and colleagues demonstrated that curcumin causes apoptosis and consequently suppresses cell growth. In MCF-7 cells, the combination of curcumin and paclitaxel led to a greater level of apoptosis than either drug used alone (35).
Curcumin analogues have been created and tested for their ability to fight tumours.

Importantly, the anti-breast cancer properties of two brand-new, non-toxic curcumin analogues, 5-bis(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidine (PAC) and 1,7-bis(4-hydroxy-3-ethoxyphenyl)-1,6-heptadien-3,5-diene
(EAC), have been studied (Figure 4). The findings showed that these analogues outperform curcumin in terms of blood stability, water solubility, bioavailability, and biodistribution (36). They were also five times as effective than curcumin in causing breast cancer cells to die off.

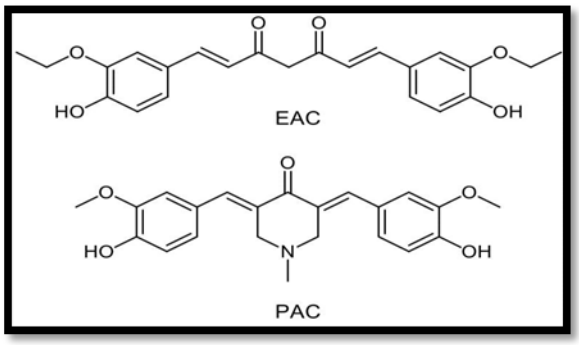

Figure 4: Curcumin analogues with potent activity versusbreast cancer

- **LUNG CANCER**

With a high percentage of morbidity and death, lung cancer is one of the most hazardous cancer kinds in the world. In around 85% of all. Non-small cell lung cancer (NSCLC) is a subtype of lung cancer. Two thirds of NSCLC cases are detected at a late advanced stage, making tumour therapy challenging owing to medication resistance (37).

Curcumin appears to be a suitable contender since there is a high need for effective adjuvant chemotherapies to strengthen the already established treatment regimens and reduce side effects and toxicity without sacrificing therapeutic efficacy (38).

Numerous studies have demonstrated that curcumin inhibits the activation of NF-kB.

This nuclear factor can inhibit apoptosis and promote cellular transformation, proliferation, invasion, and metastasis when activated by carcinogens.radio resistance, inflammation, or chemoresistance (39).

The anticancer effects of a newly synthesized curcumin analogue (JZ534) (Figure 5) on lung cancer cell lines have been studied (40). By suppressing the development of the tumour, causing apoptosis, and increasing the expression of apoptosis-related proteins such caspase 3, Bax, and p53, it demonstrated outstanding anti-lung cancer action (41).Additionally, at the same dose, JZ534 had greater anticancer efficacy than curcumin.

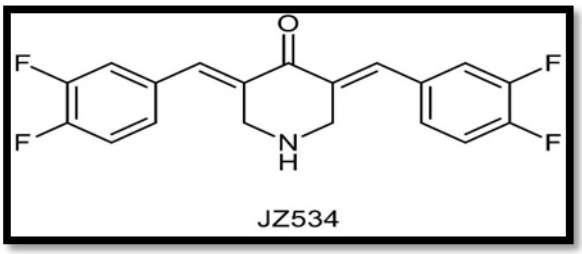

Figure 5: Curcumin analogue effective against lung cancer

- **CERVICAL CANCER**

Curcumin has been demonstrated to have antimetastatic properties and to limit the migration and invasion of cancer cells in vitro by reducing the expression and activity of several metastasis- and invasion-promoting enzymes, such as matrix metalloproteinases (MMP-2) and (MMP-9).

These enzymes accelerate metastasis by breaking down the cancer cells' extracellular matrix (42, 43). Additionally, it has been demonstrated that curcumin inhibits telomerase activity in cervical cancer, and this effect may be

superior to curcumin's other anticancer benefits in this disease (44).

The anticancer activity of EF24, a new curcumin analogue, was developed, produced, and evaluated.

Compared to curcumin, it showed more strong bioactivities and a higher bioavailability (45). Tan et alverified that EF24 is 10-20 times more effective on cervical cancer than curcumin (46).

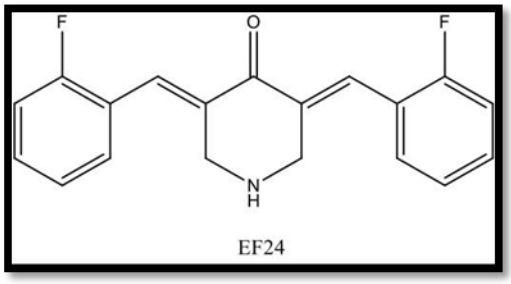

Figure 6:Curcumin analogue effective against cervicalCancer

➢ PROSTATIC CANCER

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By examining their effects on the PC3 and DU145 cells, Chen and colleagues discovered that the novel curcumin analogues RL118 and RL121 (Figure 7) exhibit a powerful cytotoxicity on the CRPC. They noted that both analogues promoted apoptosis, increased the proportion of cells in the G2/M phase of the cell cycle, and suppressed nuclear factor (NF)-$_k$B expression (49).

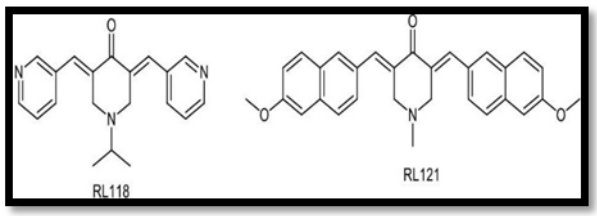

Figure 7: Curcumin analogs with an activity versus prostatic cancer

➢ PANCREATIC CANCER

In the world, deaths from cancer are linked to pancreatic cancer at a significant rate. Pancreatic cancer is responsible for 7% of all cancer-related fatalities.

Only a small amount of this cancer kind can be effectively treated with radiation and chemotherapy (50).Due to the ineffectiveness of radiation and chemotherapy un the treatment of this type of cancer, researchers have turned to other methods such the use of phytochemicals.

Difluorinated-curcumin (CDF) (Figure 8) is a curcumin derivative that has been shown in in vitro experiments to suppress the development and survival of numerous pancreatic cancer cell lines (51).

Another curcumin derivative with a greater capacity to inhibit pancreatic cell lines than curcumin is GO-Y030 (Figure 9). The capacity to reduce the survival rate of the aforementioned cell lines may depend on STAT3 inhibition (52).

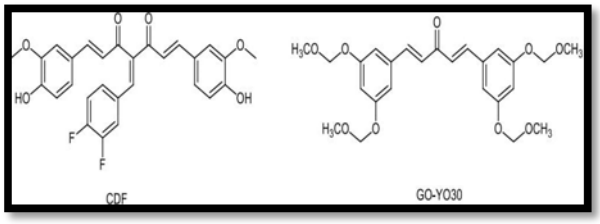

Figure 8: Curcumin derivatives with anti-pancreatic cancer activity

➢ COLORECTAL CANCER

Colorectal cancer is the fifth most prevalent kind of cancer diagnosed in underdeveloped nations, whereas it is fourth in industrialized countries. Chemo preventive drugs are one of various techniques that have been developed to prevent or postpone the carcinogenesis process (53). Several researches have proven curcumin's capacity to inhibit and slow the growth of colorectal cancer cells since 1995 (54,55).

According to a recent study by Rajitha et al, the two curcumin derivatives known as EF31 and UBS109 (Figure 9) significantly suppressed the growth of colorectal cancer cell lines by interfering with a number of different mechanisms, including the inhibition of COX-2, STAT-3, and the transcription factor NF-$_k$B. Additionally, these compounds have better water solubility, potency, and pharmacokinetic profiles than curcumin (56).

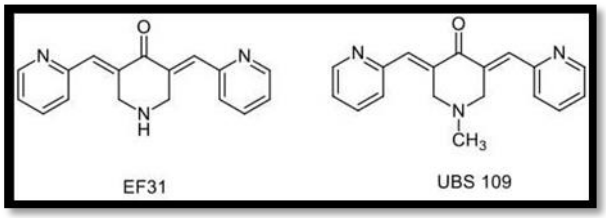

Figure 9: Curcumin derivatives which are effective against colorectal cancer

V. CONCLUSION

Turmeric contains a naturally occurring compound called curcumin, which has a wide range of pharmacological and biological activities. Unfortunately, curcumin's low oral bioavailability limits its therapeutic use. The synthesis of novel derivatives is one of the methods that have been modified to overcome this restriction. The medicinal properties of curcumin and its synthetic derivatives, including their antibacterial, anti-inflammatory andantitumor properties, have been reviewed in this work. Overall, this study showed that curcumin is a highly promiscuous molecule and may be utilized as a lead ingredient to develop and synthesis more potent molecules that would serve better in therapies in the future.

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