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Curcumin and Its Derivatives: A Review of Their Biological Activities

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ABSTRACT
Curcumin is a bright yellow phytochemical derived from the rhizome of *Curcuma longa*. Since its initial extraction from this plant, curcumin is attaining great attention from the researchers of the medical field. Curcumin possesses a wide range of biological effects such as antimicrobial, antiproliferative, antioxidant, anti-inflammatory, antidiabetic and neuroprotective activities. Such versatility makes curcumin a promising lead compound for the development of new derivatives that may have a role in the management of numerous illnesses like cancer, diabetes and Alzheimer's disease. In this paper, the focus was concentrated on some of the currently available animal and clinical studies which revealed the potential pharmacological actions of curcumin and its derivatives.

Keywords: Curcumin, Derivatives, Antimicrobial, Antioxidant, Antitumor, Anti-Alzheimer.

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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 (1). Natural product is a term which refers to any chemical substance that has been collected, extracted or isolated from living organisms (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. Despite all these difficulties, natural products still represent a significant source of compounds that have novelty in their chemical structures and modes of action (3).

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 at 430 nm while it absorbs maximally at 415 to 420 nm in acetone (6).

Curcumin (Figure 1), also known as diferuloyl methane, is a symmetric molecule. Its IUPAC name is (1E, 6E) 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with the chemical formula $C_{21}H_{20}O_6$, and the molecular weight of 368.38 g/mole (7).

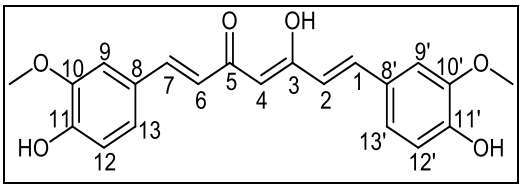

Figure 1: Chemical structure of curcumin

The safety profile of curcumin is already verified by the fact that it has been a part of the human diet in a number of countries for hundreds of years. Also, it has been used in various folks for the treatment of many diseases such as diabetes, Alzheimer's disease, cancer and rheumatoid diseases (8). It is reported that the intake of curcumin supplementation may offer a numerous health benefits, which are mostly contributed to its antioxidant and anti-inflammatory properties (9).

Although curcumin has potential therapeutic benefits exerted via anti-inflammatory and antioxidant mechanisms, the clinical applications of curcumin are limited by its low bioavailability which results from the poor water solubility, low oral absorbability, and rapid metabolic rate (10).

To tackle these drawbacks, numerous approaches have been undertaken such as the nanoencapsulation of curcumin, employment of adjuvant which interferes with its glucuronidation, and structural modification. (11) .

The aim of this study is to provide a short overview on the potential biological activities of curcumin and its currently developed derivatives, and to summarize their therapeutic effects on some of the life-threatening human diseases.

BIOLOGICAL ACTIVITIES

Antimicrobial activities

Antibacterial

Antibiotic resistance and the consequent risk of treatment failure represent a serious and growing global problem. In the developing countries, *Staphylococcus aureus* infection is a serious trouble particularly in hospitals where the

methicillin-resistant Staphylococcus aureus (MRSA) spreading is difficultly controlled (12). Over the years, the morbidity and mortality from MRSA infections were notably increasing (13). The scientists and researchers have been evoked to seek and find new compounds capable of addressing this tremendously serious problem. Recently accumulative data revealed that curcumin has exerted a potential antibacterial effect against both *methicillin-sensitive Staphylococcus aureus* (MSSA) and MRSA (14,15).
In addition to its potent antibacterial activity when used alone, curcumin also provides a marked synergistic antibacterial activity against *Staphylococcus aureus* when concurrently combined with different antibiotics such as ampicillin, ciprofloxacin, norfloxacin, gentamicin and amikacin (16). Moreover, curcumin remarkably suppresses the growth of highly pathogenic bacteria such as *Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumoniae*(17).
Numerous curcumin analogs have been synthesized and screened for their antibacterial activity. In a recently published study, a new curcumin analog named CA2 (Figure 2) was synthesized by replacing the guaiacol rings of curcumin with two halogenated coumarin rings. The afforded analog exhibited a higher aqueous solubility and more potent antibacterial activity than curcumin versus standard bacterial strains including *Pseudomonas aeruginosa, Escherichia coli*, *Klebsiella pneumonia* and *Haemophilus influenzae* (18).

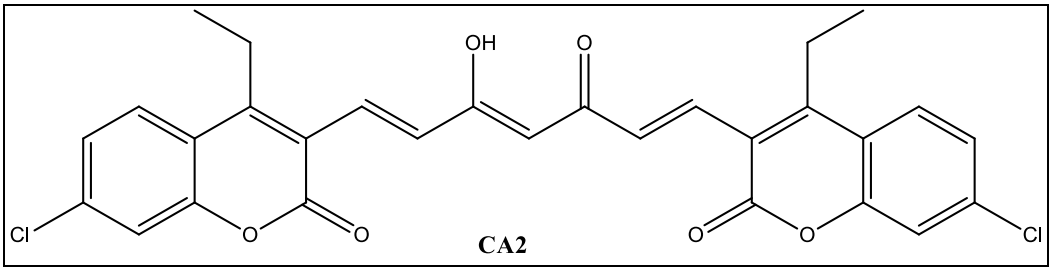

Figure 2: Curcumin analog with an antibacterial activity.

Antifungal activity
In the last few decades, spreading of the fungal infections, particularly those caused by *Candida* species, has elevated dramatically worldwide (19). *Candida albicans* is considered as the major fungal pathogen affecting humans and the most virulent pathogenic species of the genus *Candida* (20, 21).
In addition to its potent inhibitory effect on the growth of the *Candida albicans* isolates (22), curcumin is capable of attenuating the *Candida albicans* ability to resist fluconazole when concomitantly combined with this azole-based antifungal drug (23).
Two curcumin derivatives chemically titled [1,7-Bis(3,4,5-trimethoxy phenyl)-1,6-heptadiene-3,5-dione (L1) and 1,7-di(9-anthracenyl)-1,6-heptadiene-3,5-dione (L2) (Figure 3) were synthesized and tested for their antifungal activity against the following genera: *Aspergillus*, *Penicillium* and *Alternaria*. These two derivatives displayed a potential inhibitory effect on the growth of the tested cultures with superiority contributed to L1 over the other derivative (24).

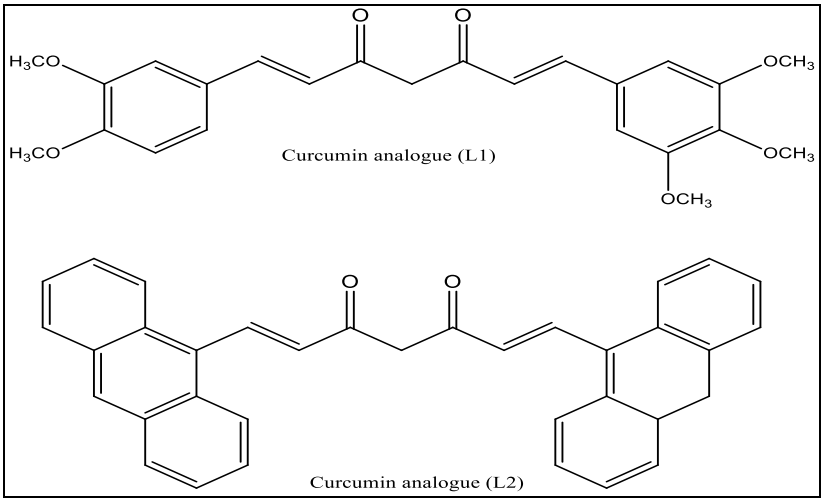

Figure 3: Curcumin derivative with a potential antifungal activity.

Antiprotozoal activity
Curcumin exerts multiple suppressive effects on the growth of many types of parasites such as *Plasmodium falciparum* (25), *Leishmania* (26), and *Giardia lamblia* (27). Furthermore, curcumin demonstrates a synergistic antiprotozoal effect when combined with artemisinin, and

an additive activity against *Plasmodium falciparum.* Also, it can enhance the survival rate of mice infected by a highly pathogenic parasite, *Plasmodium berghei* (28).

Multidrug-resistance *Plasmodium* parasites are considered as a major threat in controlling malaria, particularly those resistant to chloroquine. Nevertheless, chloroquine-resistant *Plasmodium falciparum* and artemisinin-resistant *Plasmodium chabaudi* are still sensitive to curcumin in culture and in mice respectively. These are promising data that may open the door for alternative options to control malaria (29).

Silvaa and coworkers synthesized curcumin monocarbonyl derivatives, evaluated their activity against *Trichomonas vaginalis* (causes trichomoniasis in human females), and compared their activity with metronidazole. These derivatives (3a, 3e and 5e) as displayed in Figure 4 demonstrated a potent anti-trichomoniasis activity compared to metronidazole and also they exhibited a better chemical stability and higher anti-trichomoniasis than natural curcumin (30).

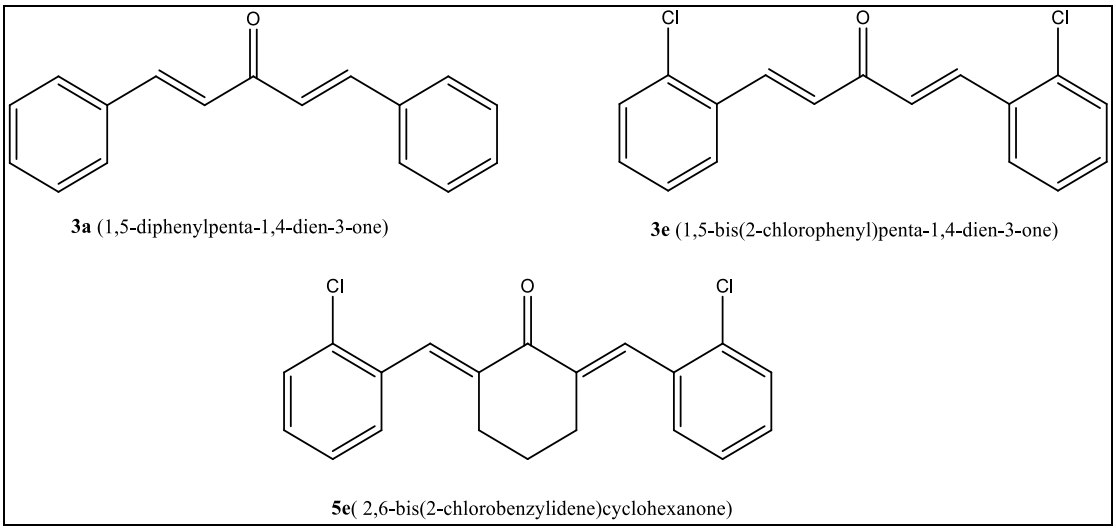

Figure 4: Curcumin analogues with potential anti-trichomoniasis activity.

Antitumor activity

Carcinogenesis is a multistep process in which numerous biochemical pathways and a huge number of mediators are upregulated. This upregulation involves enzymes, growth factors, growth factor receptors, cytokines, transcription factors, apoptosis inhibitors and proliferative enhancers. There is accumulative evidence indicating that curcumin can target many of the molecules involved in carcinogenesis like transcription factors, growth factors and their receptors which in turn regulate cell proliferation and apoptosis (31). Furthermore, curcumin has been reported to suppress the mutagenic effects of condensate results from tobacco smoking and belongs to benzo(α)pyrene (32).

Curcumin has the ability to inhibit the proliferation and induce apoptosis in several types of cancer, such as:

Breast cancer

Estrogen and its receptors alpha and beta (ER-α and ER-β) exert a vital role in the development and progression of breast cancer, which is considered the most common type of malignancy among women. Since a high percentage of patients suffering from breast cancer (two-third) have upregulated estrogen receptors, targeting of these receptors is an essential strategy for any treatment intended to suppress such tumors (33).

In a study conducted by Shao *et al*, it was verified that curcumin's antiproliferative effects are estrogen-dependent in estrogen receptor-positive breast cancer cells lines. Furthermore, this study revealed that curcumin has a powerful anti-invasive action in estrogen negative MCF-7 cells line. This action seems to be mediated by the downregulation of MMP-2 (matrix metalloproteinase) and the upregulation of TIMP-1 (tissue inhibitor of metalloproteinase), which play a critical role in the initiation and propagation of tumor cell metastasis (34).

Calaf and collaborators verified that curcumin induced apoptosis and subsequently suppressed the cell proliferation by inhibiting the assembly dynamics of microtubules and activating the mitotic checkpoint in MCF-7 cells. Combination of curcumin and paclitaxel resulted in a higher level of apoptosis in comparison with either when used alone in MCF-7 cells line (35).

A series of curcumin analogs has been synthesized and evaluated as antitumor agents. Importantly, two novel non-toxic curcumin analogs have been investigated for their anti-breast cancer property, namely 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) (Figure 5). The results revealed that these analogs have a higher stability in blood, higher water solubility, greater bioavailability and bio-distribution than that of curcumin. Also, they displayed five times higher efficiency than curcumin for inducing apoptosis in breast cancer (36).

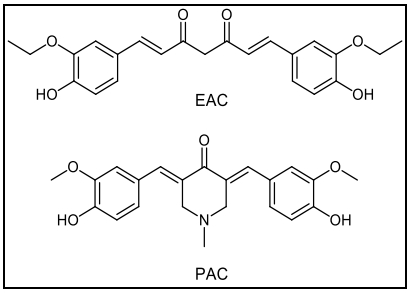

Figure 5: Curcumin analogues with potent activity versus breast cancer.

Lung cancer

Lung cancer is considered among the most dangerous cancer types worldwide with a significant high percentage of morbidity and mortality (37). Approximately 85% of all lung cancer cases belong the to non-small cell lung cancer (NSCLC) category. Two-third of NSCLC cases are diagnosed at late advanced stage rendering the treatment of tumor very difficult due to drug insusceptibility. (38). Consequently, there is great demand to develop effective adjuvant chemotherapies to fortify the currently available management protocols, and decrease the adverse effects and toxicity without compromising therapeutic efficacy; curcumin seems to be a potential candidate.

A variety of studies have shown that curcumin suppresses the activation of NF-κB. On activation by carcinogens, this nuclear factor can suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance, and/or inflammation (39,40).

A new curcumin analog (JZ534) (Figure 6) has been synthesized and investigated for its antitumor effect on the lung cancer cell lines. It exhibited an excellent anti-lung cancer activity by inhibiting the growth, inducing apoptosis and upregulating the expression of apoptosis-related proteins such as caspase 3, Bax and p53. Furthermore, JZ534 showed a higher antitumor activity than curcumin at the same concentration (41).

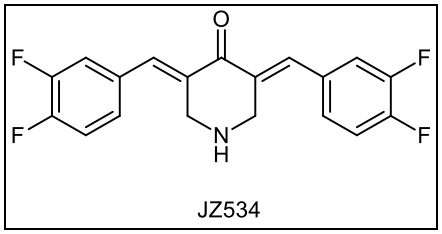

Figure 6: Curcumin analogue effective against lung cancer

Cervical cancer

It has been shown that curcumin could act as an anti-metastatic agent and inhibit cancer cell migration and invasion in vitro by decreasing the expression and activity of many enzymes that facilitate metastasis and invasion such as matrix metalloproteinases (MMP-2) and (MMP-9). These enzymes accelerate metastasis by degradation of the extracellular matrix of the cancer cells (42, 43). Besides , curcumin has been proven to inhibit telomerase activity in cervical cancer and this effect could be superior to other anticancer effects of curcumin in cervical cancer (44).

A novel curcumin analog named EF24 (Figure 7) had been designed, synthesized and tested for its antitumor activity. It displayed multiple potent bioactivities and increased bioavailability compared to curcumin (45). Tan *et al* verified that EF24 is 10-20 times more effective on cervical cancer than curcumin (46).

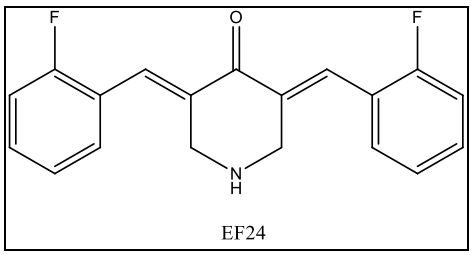

Figure 7: Curcumin analogue effective against cervical cancer.

Prostatic cancer

With early diagnosis, prostatic cancer is highly sensitive to the anti-androgen therapy but after that cancer cells begin to resist the hormonal deprivation therapy and this cancer is categorized as a castration-resistant prostate cancer (CRPC) (47).

A recent clinical study conducted on the patients with CRPC revealed that co-administration of curcumin with docetaxel caused a prostate-specific antigen (PSA) response in more than a half of the patients. PSA response was achieved in 88% of responders during the first 3 cycles of treatment (48).

Chen and colleagues have found that the new curcumin analogs RL118 and RL121 (Figure 8) have a potent cytotoxicity on the CRPC by testing their effect on the PC3 and DU145 cells. They reported that both analogs increased the number of cells in the G2/M phase of the cell cycle, induced apoptosis and inhibited the expression of nuclear factor (NF)-κB (49).

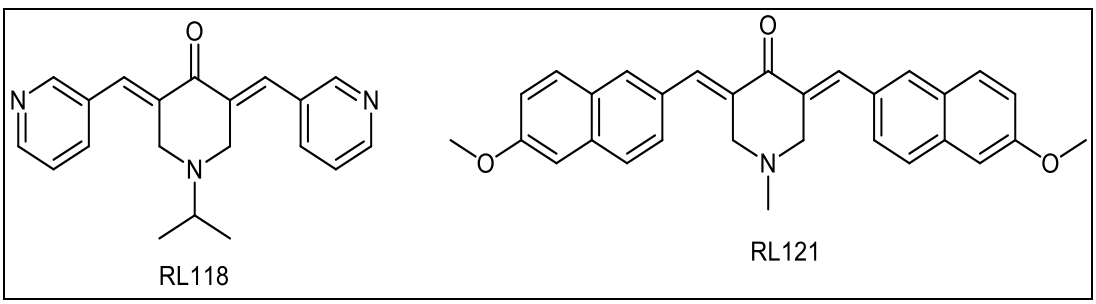

Figure 8: Curcumin analogs with an activity versus prostatic cancer.

Pancreatic cancer

Pancreatic cancer is associated with a high incidence of malignancy- related death in the world. Approximately 7% of all cancer deaths are due to pancreatic cancer. Treatment of this cancer type by radiotherapy and chemotherapy have only a limited efficacy (50).

As a result of the poor outcome of radiation and chemotherapy in treating this kind of cancer, other strategies like the applications of phytochemicals have been pursued. In vitro studies of a curcumin derivative called difluorinated-curcumin (CDF) (Figure 9) on various pancreatic cancer cell lines have proven its ability to inhibit the growth and survival of these cancer cells (51).

GO-Y030 (Figure 9) is another curcumin derivative which has a more significant ability for inhibiting the pancreatic cell lines than curcumin. This ability for suppressing the survival rate of the titled cell lines could be dependent on the inhibition of STAT3 (52)

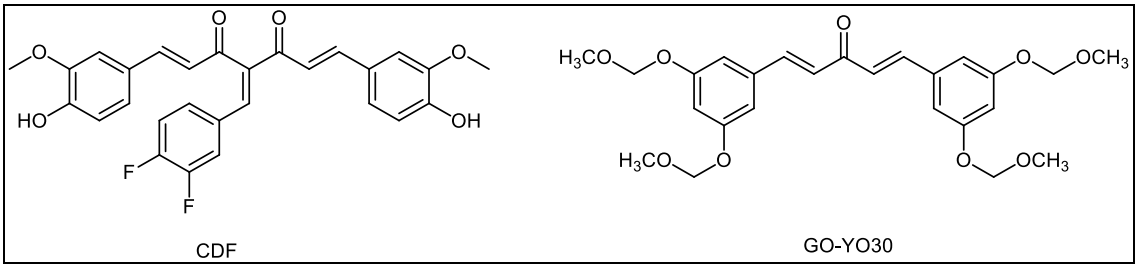

Figure 9: Curcumin derivatives with antipancreatic cancer activity.

Colorectal cancer

In the developing countries, colorectal cancer comes fifth as the most common form of the diagnosed malignancies while it comes fourth in developed countries. Chemo-preventive agents are considered one of several strategies that have been adapted to prevent or delay the carcinogenesis process (53). Since 1995, several studies have revealed the curcumin's ability to suppress and attenuate the proliferation of colorectal cancer cells (54-56).

A recent study conducted by Rajitha *et al* demonstrated that the two curcumin derivatives named EF31 and UBS109 (Figure 10) exhibited a significant suppression effect on the colorectal cancer cell lines through the interference with several mechanisms such as the inhibition of COX-2, STAT-3 and transcription factor NF-κB. Furthermore, these derivatives are superior to curcumin in terms of improved aqueous solubility, potency and pharmacokinetic profile (57)

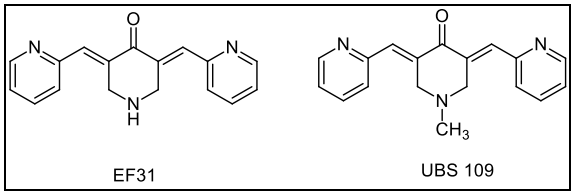

Figure 10: Curcumin derivatives which are effective against colorectal cancer.

Antioxidant activity

Oxidative stress occurs as a result of disturbance in the balance between the generation of reactive species, which are naturally produced in the human body, and endogenous antioxidants. Reactive oxygen species (ROS), formed normally during the cellular processes like cellular respiration, include superoxide radical ($O^{\cdot}{}_2^-$), hydroxyl radicals ($OH^{\cdot}$), singlet oxygen ($O^{\cdot}$) and hydrogen peroxide (H_2O_2) (58).

Overproduction of ROS can induce the oxidation of cellular components which in turn leads to tissues damage. Human body can avoid ROS damage by its own antioxidant defense systems which include superoxide dismutase (SOD), catalase (CAT) and reduced form of glutathione (GSH) (59).

Sankar and collaborators showed that free and encapsulated curcumin have the ability to indirectly upregulate the antioxidant enzymes such as SOD, CAT and glutathione reductase (60). Curcumin also exhibits a synergistic antioxidant activity when combined with the other antioxidants (61).

In the last two decades, a lot of researches have been performed to explore the antioxidant activity of curcumin and to investigate the mechanism of its free radical scavenging activity. Despite of all these efforts, the antioxidant mechanism of curcumin remains controversial. The chief argument is whether the central methylenic hydrogen in the heptadiene moiety, enolic hydrogen or the phenolic hydrogen is responsible for its antioxidant activity (62).

Jovanovic and coworkers have demonstrated that curcumin is a strong H-atom donor by donating the H-atom from the central methylenic group rather than from the phenolic group (63). In contrast to their conclusion, Barclay *et al* assumed that curcumin is a classical phenolic chain-breaking antioxidant, donating H-atoms from the phenolic group (64).

In a recently published study, several curcumin analogs had been synthesized and tested for their antioxidant activity. They showed an antioxidant activity closely related to that of curcumin despite the lack phenolic hydrogen in their chemical structures. This study proposed that the antioxidant activity of these curcumin analogs may be attributed to their ability to donate the enolic hydrogen (18).

Other researchers verified that the phenolic hydroxyl group of curcumin is essential for its free-radical scavenging activity and that the presence of methoxy group ortho to the phenolic hydroxyl group will is further increase the antiradical activity of curcumin (65).

In the last two decades, a large number of curcumin derivatives has been synthesized in order to find new compounds with a powerful antioxidant activity. Shang and colleagues synthesized three series of curcumin derivatives (Figure 11) and they evaluated their antioxidant activity in comparison with curcumin. They found that those compounds which contain O-diphenoxyl- and O-dimethoxy-phenoxyl groups exhibited a significantly higher antioxidant activity than those which bear no such groups. They also concluded that the 7-carbon spacer is essential for the scavenging properties and reducing the spacer to 5 carbon atoms greatly reduced the scavenging activity. They also suggested that lipophilicity which results from increasing the number of carbon atoms was important for the antioxidant activity (66).

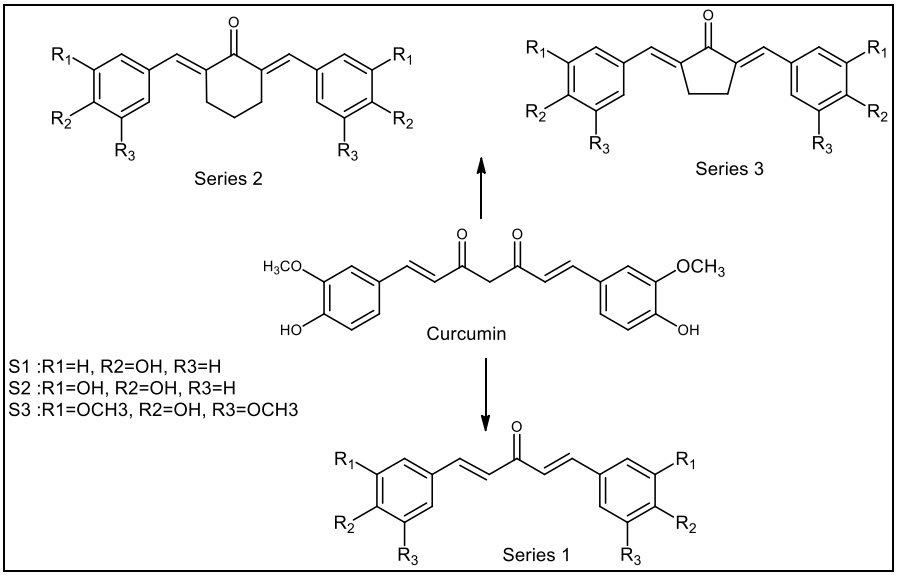

Figure 11: Series of curcumin derivatives with an antioxidant activity.

Anti-inflammatory activity

Inflammation plays a vital role in the pathogenesis of numerous diseases such as cardiovascular diseases (67), cancer (68), diabetes (69) and neurodegenerative disorders (70). In addition to other mediators, NF-κB exerts a critical role in the signal transduction pathways, which are involved in the inflammatory diseases. Therefore, NF-κB is thought to be a promising therapeutic target for these diseases (71).

A series of studies verified that curcumin has an anti-inflammatory effect by the suppression of NF-κB to a significant degree (72-81). Other studies revealed that curcumin is responsible for the downregulation of various inflammatory cytokines such as TNF, IL-1, IL-6, IL-8, interferon and some other chemokines (82-84).

Paulino and coworkers prepared a curcumin analog (DM1) (Figure 12) and evaluated its effect on the inflammatory mediators and they reported that this analog has the ability to suppress the iNOS and COX2 (85).

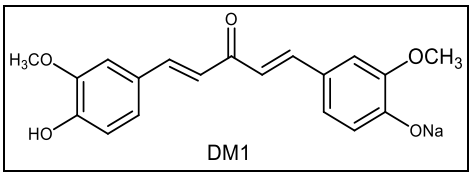

Figure 12: Curcumin analog with a potent anti-inflammatory effect.

Antidiabetic activity

To date, there have been accumulative animal studies that strongly recommended the potential therapeutic effect of curcumin in the management of diabetes mellitus through its hypoglycemic, hypolipidemic, antioxidative, and anti-inflammatory effects. Curcumin may enhance insulin sensitivity through interference with several processes; firstly, by stimulating glucokinase activity in the liver, and subsequently improving the glucose homeostasis. Secondly, it can reduce hypertriglyceridemia by activating the lipoprotein lipase activity for reducing both triglyceride and VLDL. Thirdly, it can facilitate the extrahepatic glucose uptake via the induction of glucose transporter-4 (GLUT4) expression (86).

A study performed by Kim and colleagues stated that the glucose-lowering effects of curcumin could be due to reduction of hepatic glucose output through suppression of gluconeogenesis (87). Furthermore, curcumin was also endorsed to attenuate diabetic micro and macro-vascular complications like diabetic nephropathy (88), cardiomyopathy (89) and retinopathy (90).

Anti-Alzheimer activity

Alzheimer's disease (AD) is a common progressive neurodegenerative brain disease which remains without an effective curative therapy. Despite of its development as a consequence of numerous factors rather than a single cause, its etiology and pathology remain unclear. The key

pathological feature observed in AD is the aggregation of extracellular amyloid plaques which is termed Aβ aggregation. Accumulative data have implicated the role of biometals like iron, copper and zinc in Aβ aggregation deposition and production of ROS and the widespread oxidative damage observed in the brains of patients suffering from AD (91). Considering the multifactorial etiology and complex pathological mechanisms of AD, there is an urgent demand for searching the therapeutic agents with pleiotropic activity targeting several affected processes (92). Among these compounds that fulfill these properties, curcumin has been reported to exhibit a strong anti-Aβ property with considerable anti-inflammatory and antioxidant activities (93).

A series of curcumin derivatives had been synthesized by Chen and collaborators and evaluated for their efficacy in the management of AD. These derivatives exhibited a superior inhibitory activity against Aβ aggregation over curcumin. Also, they showed superiority over the reference compound Trolox as antioxidants, chelators for metals (iron and copper) and suppressors of the metal induced Aβ aggregation. Further investigations confirmed that the derivative named A4 (Figure 13) displayed better results than the tested curcumin derivatives and these results were highly suggested a further structure optimization for A4 to develop more potent multifunctional anti-Alzheimer agents (92).

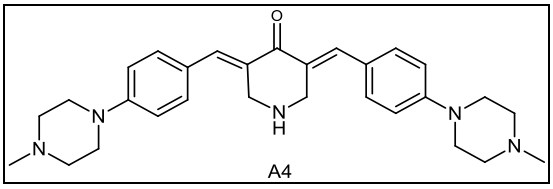

Figure 13: Curcumin derivative with a potent anti-Alzheimer activity.

CONCLUSION

Curcumin is a natural substance acquired from turmeric with a large variety of pharmacological and biological activities. Unfortunately, the clinical usefulness of curcumin is limited due to its poor oral bioavailability. To address this limitation, several approaches have been adapted; one of them is the synthesis of new derivatives. In this study, the therapeutic activities of curcumin and its synthesized derivatives such as antimicrobial, antitumor, antioxidant, anti-inflammatory, antidiabetic and neuroprotective properties have been reviewed. Overall, this study concluded from the described studies that curcumin is a highly promiscuous molecule and can be used as a lead compound to design and synthesize new effective compounds which can serve better in therapeutics prospectively.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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