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CURCUMIN: FROM A MOLECULAR STRUCTURE TO A PHTOSENSTIZER

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ABSTRACT Multi-drug resistant bacteria are a significant global public health issue today. New antibacterial techniques have been created to combat it. One of these is antimicrobial photodynamic treatment, which is effective against a range of microorganisms in various medical and healthcare settings.The interplay of a photosensitizer, molecular oxygen, and a suitable light source forms the foundation of the antimicrobial photodynamic technique. Here, we discussed the primary physical and chemical characteristics of curcumin, a practical natural photosensitizer, including its pathways for degradation, analytical techniques for quantification, extraction method, synthesizing techniques, and employed pharmaceutical formulations. The use of curcumin as a photosensitizer against microorganisms is also put up and covered in a comprehensive scientific review.

KEYWORDS : Curcumin, Photosensitizer, Photodynamic Therapy, Reactive Oxygen Species

INTRODUCTION

The perennial herb turmeric, Curcuma longa Linn., is farmed primarily in south and southeast tropical Asia. It is a member of the Zingiberaceae family, which also includes ginger. The most beneficial component of this plant is its rhizome, which is also known as its root and has been used as a spice in food for generations. To treat a number of illnesses, it has been applied topically and orally. It is frequently used to treat hepatic problems, anorexia, cough, diabetic wounds, rheumatoid arthritis, and sinusitis in conventional Indian Ayurvedic medicine. An effective home remedy for the treatment of inflammation and wounds is turmeric paste with slaked lime. Curcumin is mentioned in ancient Indian medical books as being used to treat stomach issues, wounds, and inflammatory disorders. [1].

The combination of chemical substances and light is attributed to Oscar Raab in 1900, which accidentally promoted protozoan killing after a photo biological reaction that was later found to be an oxygen dependent phenomenon [2].

However, with the invention of antibiotics in 1928, research on the 'photodynamic therapy's' antibacterial potency gradually dropped. The creation of efficient cancer management regimens has been the focus of photodynamic therapy (PDT). Combining a medication called a photo sensitizer (PS) with the delivery of light at the right wavelength to stimulate the PS molecule is the basis of a photodynamic process. [3].

The PS absorbs photons and induces a series of reactions involving the formation of radicals and reactive oxygen species (ROS). Nowadays, PDT has been recognized as an effective treatment for various localized premalignant conditions and solid tumors [4].

More recently, growing antibiotic resistance has demanded the re assessment of antimicrobial PDT, particularly for superficial infections wherein the contact with light is facilitated [5].

Numerous investigations started to study PDT against microorganisms (MOs) [6–8], and suggested this therapy in cases of microbial resistance or in association with the existing drugs to enhance its effectiveness [9]. Photodynamic inactivation of MOs is also known as Photodynamic Antimicrobial Chemotherapy (PACT) [5] or Photodynamic Inactivation (PDI) [10]. Since the ROS can react with non-specific targets, PDI carries several advantages over conventional antibiotics and antifungals, for example, few undesired side effects and little likelihood of promoting the development of resistance by micro-organisms [11].

The literature reports the existence of synthetic and natural pigments that can be used as PS for PDT and PDI [5,12]. Despite the higher stability present by the synthetic dyes, natural compounds have been largely studied and accepted, mainly because they are less prone to collateral effects and drug interactions [6,7,13].

In this review, we discussed the key ideas behind PDT, including its origins, workings, and uses against microbes and the fight against antibiotic resistance. Along with descriptions and discussions of the general physical and chemical properties of curcumin-PS, including its extraction and synthetic methodologies, pharmaceutical formulations, and degradation pathways, a thorough review of the prior years' work on the use of curcumin as a PS and antimicrobial agent was also conducted.

History and mechanism of photodynamic therapy (PDT):

Ancient civilizations (~3000 BC) already used sunlight to treat various skin conditions. Perhaps, this was the first clinical protocol involving light interaction with biological tissues, but in an empirical way [14].

In 1877, in England, Arthur Downes and Thomas Blunt showed that the wavelengths of the sun in the ultraviolet region are lethal to bacteria and other microorganisms, thus being one of the bases for phototherapy [15]. A Nobel laureate who was the pioneer of the application of phototherapy in modern clinical practice: Niels Ryberg Finsen, in 1903 showed that the use of light emitting in the red region of the visible spectrum healed lesions of smallpox patients and prevented suppuration [16].

It is well documented fact that the Professor Finsen who was the Director of the Finsen Medical Light Institute of Copenhagen turned to the “real phototherapy”, in particular to the treatment of tubercular skin infections (lupus vulgaris). As a light source, he first used the sun and designed devices containing quartz lenses and filters that removed infrared and visible radiations and concentrated the bactericidal ultraviolet component in the lesion to be treated. His student Oscar Raab observed the potential use of light-sensitive chemicals

compounds (photosensitizers) as toxic agents for biological systems in presence of light. He noted that this dye had a higher toxic effect on paramecium samples on sunny days than on cloudy days, then making this association of the photodynamic action of a photo sensitizer in the presence of energy from a source, in this case the bright sun [17]. Moreover, one of the most cited and famous photos of the phototoxic effects of systemically administered porphyrins (200 mg intravenously) was taken in 1913 and published at Therapeutische versuche mit fluoreszierenden Stoffen [18] showing the German doctor Friedrich Meyer Betz with significant edema and hyperpigmentation for more than two months after hematoporphyrin self-injection. In 1960, Lipson and collaborators studied and reported hematoporphyrin derivative (HpD) synthesis by treating hematoporphyrin chloride with hydrochloric and sulfuric acid. The development of HpD established the basis of today's PDT [19]. Preliminary studies were quickly expanded to investigate the efficiency of HpD in both preclinical and clinical studies in the 1970s [20]. An effort led by Dougherty to prepare a drug grade HpD in large scale following the FDA regulations produced the Photofrin®, the first approved photosensitizer drug, in 1993 [21].

The PS agent in its ground state is a singlet PS, which has two electrons with opposite spins and the total spin is zero, thus given the term symbol S0 (for the exception of molecular oxygen). Absorption of light with the appropriate wave length (quantum energy) leads to the excitation of one electron into a higher-energy orbital (I). Due to the instability of singlet excited-state PS, it may lose its excess energy by emission of light (fluorescence process) or producing heat by internal conversion. However, the singlet excited-state PS may undergo a process known as intersystem crossing (IC), forming a more stable and triplet excited-state with parallel spins (II). In this state, the spin angular momentum of two unpaired electrons adds up to a spin quantum number of 1. In this step, the triplet excited-state PS that may decay back to the ground state by emitting a phosphorescent photon, but this is a 'forbidden process' by the quantum selection rules. The triplet state is much more stable than the singlet state having a lifetime of microseconds compared with only nanoseconds for the singlet excited-state PS. Then, the long lifetime of the triplet state transfers its energy (type II mechanism) to O2, which is unique in being a molecular triplet in its ground state, forming singlet oxygen (1O2). Moreover, the photodynamic process can undergo type I mechanism via electron transfer reactions forming reactive oxygen species (ROS) namely superoxide radical anion (O2 −), hydrogen peroxide (H2O2), and hydroxyl radicals (HO) (III). Thus, the ROS and1O2 produced can cause oxidative stress in the biomolecules targeting mainly at cancer cells and pathogenic microorganisms. The affected biomolecules include lipids, nucleic acids and proteins [22,23].

Chemistry Of Curcumin:

The marked yellow colour of turmeric is due to the presence of curcuminoids which essentially contain curcumin. Commercially curcumin is a mixture of three curcuminoids. (A) 71.5% curcumin (Curcumin 1) mixture of three (B) 19.4% demethoxycurcumin (Curcumin 2) (C) 9.1% bisdemethoxycucumin (curcumin 3). These three major curcuminoids are also found in some other species of Curcuma but lesser concentration – e.g- C.amada, C. aromatic some minor and rare curcuminoids of C.longa or their analogues may be identified in other species e.g, cyclo-curcumin with cyclization of seven carbon units as a ring found in C. longa. Curcuminoids have shown different activities. A recent study suggests that curcumin had a relatively higher potency for suppression of tumour necrosis factor (TNF-α) induce nuclear factor-κβ activation than that of demethoxycurcumin and bisdemethoxycurcumin. This suggests that the methoxy group on the phenyl ring has a critical role but conjugated bond in the central seven carbon chain is also important for curcuminoids NF-κβ activity. However, the suppression of proliferation of various tumour cells lines by curcumin, demethoxycurcumin, and bis-demethoxycurcumin was found to be comparable; indicating the methoxy group plays a minimum role in the anti-proliferative effects of curcuminoids [24, 25].

The chemical formula of the main three principal derivative of curcumin are: -

(A) Curcumin 1:- chemical formula- C21H20O6 (Molecular weight=368)

(B) Curcumin 2:- chemical formula C20H18O5 (Molecular weight=338)

(C) Curcumin 3:- chemical formula C19H16O4 (Molecular weight=308)

A minor amount of oil may be naturally present in curcumin. The predominant constituent of this oil appears to be sesquiterpene ketone and alcohol, α-turmerone, β turmerone, m-eugenol, turmerone-A, turmerone–B.

Biological property of curcumin

The Curcumin affect Angiogenesis C. longa which has been used to treat a variety of ailments since prehistoric times. Turmeric and ginger its active ingredients are multi-targeted phytochemicals for the treatment of cancer. Apoptosis, for example, is a type of cell death. Their use can alter autophagy and cell cycle halt.

1) Colorectal Cancer (CRC) has recently emerged as a serious public health concern. Obesity and its associated metabolic issues have been linked to colorectal carcinogenesis, according to research. There have been numerous biological mechanisms discovered in the relationship between obesity and the progression of CRC. As a result, turmeric's regulation of the NF-κB and STAT-3 pathways can effectively hinder tumour cell proliferation.

2) Hepatic cancer is another type of complicated disease in which human hepatoma SMMC-7721 cells are affected. Curcumin inhibits the development of SMMC-7721 cells by triggering apoptosis via modification of the bax/bcl-2 pathway. Curcumin stimulates the apoptotic pathway and inhibits cell growth and proliferation, resulting in cell death.

Anti-diabetic activity:-

Curcumin has been shown to have anti-diabetic properties. Curcumin's antioxidant properties may be responsible for its anti-diabetic properties. Curcumin has been shown in recent research to have the ability to directly quench reactive oxygen species (ROS), which can contribute to oxidative damage. This feature is thought to contribute to curcumin's overall protective benefits. Curcumin can help prevent cell death caused by oxidative stress by inducing and/or activating antioxidant/cytoprotective enzymes like heme oxygenase 1 (HO-1). Curcumin was tested in a pre-diabetic human population for its ability to prevent type 2 diabetes [26].

Wound healing activity: -

Wound healing is a complex process that involves inflammation, granulation, and tissue remodelling. Curcumin-treated wounds had higher immune histochemistry localization of transforming growth factor-1 than untreated wounds, modifying collagen, and reducing reactive oxygen species. Early re-epithelialization, enhanced neovascularization, greater migration of numerous cells into the wound bed, including dermal myofibroblasts, fibroblasts, and macrophages, and higher collagen content were all seen with curcumin.

Anti-angiogenesis activity: -

Pathological angiogenesis is a sign of cancer and several ischemic and inflammatory diseases. In recent years, significant progress has been made in understanding the process of angiogenesis in many pathophysiological conditions. Curcumin inhibits angiogenesis directly, while also inhibiting the expression of numerous pro-angiogenesis factors. Curcumin has an anti-angiogenesis action. Curcumin inhibits angiogenesis directly while also inhibiting the expression of numerous pro-angiogenesis factors. Curcumin impacts the entire process of angiogenesis by downregulating transcription factors like NF-κB and pro-angiogenesis factors like Vascular Endothelial Growth Factor (VEGF), b Fibroblast Growth Factor (bFGF), and Matrix Metalloproteinase (MMPs) all of which are associated with cancer and are involved in curcumin's convoluted regulating process [27-29].

Anti-arthritis activity: -

Rheumatoid arthritis (RA) is an auto immune disease in which there is joint inflammation, synovial proliferation, and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines, mainly Tumor Necrotic Factor- alpha (TNF-α), Interleukin-1 (IL-1) which are chemotactic for neutrophils. Curcumin's antioxidant, anti-proliferative, anti-inflammatory, and immune-suppressive properties are thought to help individuals with rheumatoid arthritis relieve their symptoms. Reduced apoptosis could be one of the most serious outcomes of RA. Curcumin inhibited the development of synovial fibroblasts and induced apoptosis when they were exposed to it. These findings suggest that curcumin may aid in the

prevention of synovial fibroblast hyperplasia in RA [30].

Anti-oxidant activity: -

Curcumin is a unique antioxidant that includes the B-keto group, carbon-carbon double bonds, and phenyl rings with different quantities of hydroxyl and methoxy substituents. The enol form of curcumin is substantially more stable than the di-keto form, and the bond dissociation enthalpy (BDE) of the phenolic O: H bond is significantly lower than the BDE of the central O: H bond, implying that hydrogen atom abstraction occurs in the phenolic group. The relative contribution of the phenolic group and the core methylenic group to antioxidant activity is also dependent on the attacking radical's activity and the reaction media.

Anti-inflammatory activity: -

Curcumin has been discovered to have amazing anti-inflammatory properties. Curcumin's natural anti-inflammatory action is comparable to that of steroidal and nonsteroidal medications such as indomethacin and phenylbutazone, both of which have serious side effects negative consequences. It appears to have anti-inflammatory properties via inhibiting Cyclooxygenase-2 (COX-2), Lipooxygenase (LOX), Non-selective nitric oxide synthase (NOS), and the generation of cytokines like interferon and tumor necrosis factor, as well as activating transcription factors like Nuclear factor κB (NF-κB) and Activator protein (AP-1) [25].

Anti-bacterial activity: -

Curcumin has been shown to reduce the growth of periodontal bacteria and Porphyromonas gingivitis Arg- and Lys-specific proteinase (RGP and KGP, respectively) activities in antibacterial research. Curcumin also inhibited the production of P. gingivitis homotypic and Streptococcus gordonii biofilms in a dose-dependent manner. Curcumin at a dosage of 20 g/mL reduced the production of P. gingivitis biofilms by more than 80%. After treatment with curcumin at the Minimum inhibitory concentration, various characteristics of a bacterial apoptosis-like response were identified, including membrane depolarization, Ca2+ influx, PS exposure, and DNA fragmentation. Curcumin induces a bacterial apoptosis like response by generating reactive oxygen species production and DNA damage.

Photoactivation of curcumin

Curcumin with wide therapeutic applications [31] has proved be biologically safe and has a broad absorption peak in the range of 300-500 nm (maximum ×430 nm) with potent phototoxic effects in micromolar concentrations. Indeed, the PS effects of curcumin are reported to be beneficial in the treatment of localized superficial infections in the mouth or skin.[32] The antimicrobial activity of PS is extensively documented in the literature [33-35] as it offers low-cost therapy, simple manipulation procedures, and greater effectiveness

PDT was done with a blue halogen curing light of wavelength 470 nm with intensity 620 mW/cm2, a continuous mode for 5 min. adjunctive use of curcumin gel as a local sub-gingival drug with SRP has an antibacterial action on periodontal pathogens such as Aa, Pg, and Pi.

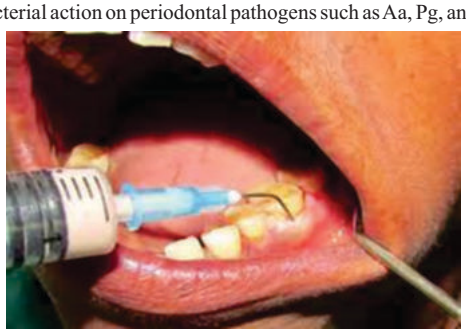

Figure 1: Local delivery of curcumin

Photoactivation of nanocurcumin (in vitro effects): More than 750 types of bacteria or phylotypes are detected in oral cavity. Despite the fact, that human immune system constantly monitors their growth and reproduction, some of the bacteria in the mouth are responsible for oral diseases such as caries and periodontal diseases, which are one of the most common diseases in humans. In last years, devices emitting laser beam in blue spectrum has been the subject of substantial research also in dentistry [36]. Previous investigations demonstrated phototoxic effect of blue light for effectively reducing some pathogens. But improvement of bactericidal effect might be theoretically possible using exogenous chromophore under the terms of PTT [37]. With respect to the color, curcumin seems be a suitable chromophore for this method. In addition to this activity, anti-inflammatory, antioxidant, chemo preventive and chemotherapeutic abilities may be beneficial in suppression of inflammatory reactions.

Important criterion of effectivity of photothermal reaction is accessibility and contact of bacteria with photosensitizer. Because curcumin shows poor solubility in water, we decided to use curcumin nanoparticles and evaluate their effect as a photosensitizer for 445 nm laser in effectiveness against selected G^+ and G^- bacteria in vitro.

Curcumin nanoparticles preparation: Ultrasonically-assisted liquid antisolvent precipitation was used for nanoparticles preparation. Stock of curcumin solution (5 mg/ml) was prepared by dissolving curcumin powder (Sigma Aldrich) in 90% ethanol (sample E) or acetone (sample A) (20 ml). One ml of stock solution was added to boiling water (50 ml) in drop-wise manner under ultrasonication condition with frequency of 50 kHz. The solution was sonicated for 30 min. After sonication, the mixture was stirred at 800 rpm for 20 min till the orange-coloured precipitate was obtained. Thereafter, supernatant was discarded and the pellet obtained was used for further study. Before application on the surface of solid cultivation media 100 mg of curcumin nanomaterial was dissolved in 1 ml of 0,9% saline solution. Parallelly, nanoparticles without sonication were prepared as well. 100mW power, irradiation time 1 min, fibre diameter 0,3 mm, distance of fibre from the surface 15 mm, energy density 7,68 J/cm^2. After 48 hours of anaerobic cultivation at 37^{o}C the antibacterial effect was evaluated.

CONCLUSION:

Over the past few years, curcumin delivery methods using nanotechnology have been researched. The development of a wide variety of new formulations, such as nano-curcumins, has mostly been restricted to in vitro cancer models. However, recent research has indicated that the formulations may potentially be used to treat infectious disorders.

PDT has been a potential therapeutic approach for the management of both malignant and non-malignant disorders over time. Due to the rise of microorganisms that are resistant to antifungal and antibacterial drugs, various studies investigating the use of PDI for decreasing germs are now being conducted. Experiments conducted in vitro and in vivo revealed that when the method is combined with blue LED light irradiation, modest curcumin (CUR) concentrations are sufficient for the photodynamic efficacy against tumor cells and bacteria.

Despite the fact that the effectiveness of CUR-mediated PDT/PDI has been generally confirmed, the studies have produced a variety of different results. These variations may be attributed to the variety of CUR concentrations used, the variety of CUR solvents used, the type of CUR used, the distinct PITs used, the variety of microorganism species evaluated, as well as the different strains within the same species, the growth mode of the microorganisms (planktonic or biofilm), Therefore, it may be challenging to compare the effectiveness findings when the factors are completely different. There are a lot of in vitro studies that demonstrate the potential of the CUR-mediated PDT/PDI, and their results mark significant advancements in this field. However, the only way to firmly establish an efficient methodology is through in vivo experiments. Therefore, in situ and in vivo studies are required to develop a PDI methodology that may be employed safely in clinical settings. Gram-positive and Gram-negative bacteria, fungi, viruses, and protozoa have lessened their viability due to the use of curcumin as a PS in various antimicrobial photo dynamic procedures. This effect has been seen in a variety of application areas. Therefore, it can be challenging to compare and interpret these presented results due to the range of parameters employed for antimicrobial photodynamic treatments using curcumin as PS. We do anticipate that using curcumin and its equivalents as PS will enhance the current photodynamic procedures for the treatment of infectious diseases, the cleaning of surfaces, and food safety.

REFERENCES

1) Ammon, H. P., & Wahl, M. A. (1991). Pharmacology of Curcuma longa. Planta medica, 57(1), 1–7.
2) Moan, J., & Peng, Q. (2003). An outline of the hundred-year history of PDT. Anticancer research, 23(5A), 3591–3600.
3) Henderson, B. W., & Dougherty, T. J. (1992). How does photodynamic therapy work?. Photochemistry and photobiology, 55(1), 145–157.
4) Vohra, F., Al-Kheraif, A. A., Qadri, T., Hassan, M. I., Ahmed, A., Warnakulasuriya, S., &

Javed, F. (2015). Efficacy of photodynamic therapy in the management of oral premalignant lesions. A systematic review. Photodiagnosis and photodynamic therapy, 12(1), 150–159.
5) Andrade, M. C., Ribeiro, A. P., Dovigo, L. N., Brunetti, I. L., Giampaolo, E. T., Bagnato, V. S., & Pavarina, A. C. (2013). Effect of different pre-irradiation times on curcumin-mediated photodynamic therapy against planktonic cultures and biofilms of Candida spp. Archives of oral biology, 58(2), 200–210.
6) Dovigo, L. N., Pavarina, A. C., Carmello, J. C., Machado, A. L., Brunetti, I. L., & Bagnato, V. S. (2011). Susceptibility of clinical isolates of Candida to photodynamic effects of curcumin. Lasers in surgery and medicine, 43(9), 927–934.
7) Araújo, N. C., Fontana, C. R., Bagnato, V. S., & Gerbi, M. E. (2012). Photodynamic effects of curcumin against cariogenic pathogens. Photomedicine and laser surgery, 30(7), 393–399.
8) Paschoal, M. A., Lin, M., Santos-Pinto, L., & Duarte, S. (2015). Photodynamic antimicrobial chemotherapy on Streptococcus mutans using curcumin and toluidine blue activated by a novel LED device. Lasers in medical science, 30(2), 885–890.
9) Sbarra, M. S., Di Poto, A., Arciola, C. R., Saino, E., Sharma, M., Bragheri, F., Cristiani, I., Speziale, P., & Visai, L. (2008). Photodynamic action of merocyanine 540 on Staphylococcus epidermidis biofilms. The International journal of artificial organs, 31(9), 848–857.
10) Pereira Gonzales, F., & Maisch, T. (2010). Photodynamic inactivation of microorganisms as an innovative approach to kill mucocutaneous and skin microorganisms. Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia, 145(4), 477–489.
11) Goulart, R.D., Bolean, M., Paulino, T.P., Thedei, G., Souza, S.L., Tedesco, A.C., & Ciancaglini, P. (2010). Photodynamic therapy in planktonic and biofilm cultures of Aggregatibacter actinomycetemcomitans. *Photomedicine and laser surgery, 28 Suppl 1*, S53-60 .
12) Leite, D. P., Paolillo, F. R., Parmesano, T. N., Fontana, C. R., & Bagnato, V. S. (2014). Effects of photodynamic therapy with blue light and curcumin as mouth rinse for oral disinfection: a randomized controlled trial. Photomedicine and laser surgery, 32(11), 627–632.
13) Lai, J., & Cooney, M. (1999). History of photodynamic therapy. International ophthalmology clinics, 39(4), 163–174.
14) McDonagh A. F. (2001). Phototherapy: from ancient Egypt to the new millennium. Journal of perinatology : official journal of the California Perinatal Association, 21 Suppl 1, S7–S12.
15) Finsen N. R. (1903). REMARKS on the RED-LIGHT TREATMENT of SMALL-POX: Is the Treatment of Small-pox Patients in Broad Daylight Warrantable?. British medical journal, 1(2214), 1297–1298.
16) Tappeiner, H.V. (1909). Die photodynamische Erscheinung (Sensibilisierung durch fluoreszierende Stoffe). *Ergebnisse der Physiologie, 8*, 698-741.
17) Dougherty, T. J., Gomer, C. J., Henderson, B. W., Jori, G., Kessel, D., Korbelik, M., Moan, J., & Peng, Q. (1998). Photodynamic therapy. Journal of the National Cancer Institute, 90(12), 889–905.
18) Huang Z. (2005). A review of progress in clinical photodynamic therapy. Technology in cancer research & treatment, 4(3), 283–293.
19) Dolmans, D. E., Fukumura, D., & Jain, R. K. (2003). Photodynamic therapy for cancer. Nature reviews. Cancer, 3(5), 380–387.
20) Jabłoński, A. (1933). Efficiency of Anti-Stokes Fluorescence in Dyes. *Nature, 131*, 839-840.
21) Castano, A. P., Demidova, T. N., & Hamblin, M. R. (2004). Mechanisms in photodynamic therapy: part one-photosensitizers, photochemistry and cellular localization. Photodiagnosis and photodynamic therapy, 1(4), 279–293.
22) Robertson, C. A., Evans, D. H., & Abrahamse, H. (2009). Photodynamic therapy (PDT): a short review on cellular mechanisms and cancer research applications for PDT. Journal of photochemistry and photobiology. B, Biology, 96(1), 1–8.
23) Szlosarek, P., Charles, K. A., & Balkwill, F. R. (2006). Tumour necrosis factor-alpha as a tumour promoter. European journal of cancer (Oxford, England : 1990), 42(6), 745–750.
24) Yadav, V. R., Prasad, S., Kannappan, R., Ravindran, J., Chaturvedi, M. M., Vaahtera, L., Parkkinen, J., & Aggarwal, B. B. (2010). Cyclodextrin-complexed curcumin exhibits anti-inflammatory and antiproliferative activities superior to those of curcumin through higher cellular uptake. Biochemical pharmacology, 80(7), 1021–1032.
25) Norrby K. (2002). Mast cells and angiogenesis. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica, 110(5), 355–371.
26) Huang, X. F., & Chen, J. Z. (2009). Obesity, the PI3K/Akt signal pathway and colon cancer. Obesity reviews : an official journal of the International Association for the Study of Obesity, 10(6), 610–616.
27) Klagsbrun, M., & Moses, M. A. (1999). Molecular angiogenesis. Chemistry & biology, 6(8), R217–R224.
28) Folkman J. (1995). Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. The New England journal of medicine, 333(26), 1757–1763
29) Folkman J. (1995). Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature medicine, 1(1), 27–31.
30) Folkman, J., & Klagsbrun, M. (1987). Angiogenic factors. Science (New York, N.Y.), 235(4787), 442–447.
31) Zanin, I. C., Lobo, M. M., Rodrigues, L. K., Pimenta, L. A., Höfling, J. F., & Gonçalves, R. B. (2006). Photosensitization of in vitro biofilms by toluidine blue O combined with a light-emitting diode. European journal of oral sciences, 114(1), 64–69.
32) Komerik, N., & MacRobert, A. J. (2006). Photodynamic therapy as an alternative antimicrobial modality for oral infections. Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer, 25(1-2), 487–504.
33) Kim, G. Y., Kim, K. H., Lee, S. H., Yoon, M. S., Lee, H. J., Moon, D. O., Lee, C. M., Ahn, S. C., Park, Y. C., & Park, Y. M. (2005). Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. Journal of immunology (Baltimore, Md. : 1950), 174(12), 8116–8124.
34) Carvalho, L. H., D'Avila, G. B., Leão, A., Gonçalves, C., Haffajee, A. D., Socransky, S. S., & Feres, M. (2005). Scaling and root planing, systemic metronidazole and professional plaque removal in the treatment of chronic periodontitis in a Brazilian population II--microbiological results. Journal of clinical periodontology, 32(4), 406–411.
35) Wilson, M., Burns, T., & Pratten, J. (1996). Killing of Streptococcus sanguis in biofilms using a light-activated antimicrobial agent. The Journal of antimicrobial chemotherapy, 37(2), 377–381.
36) Shany-Kdoshim, S., Polak, D., Houri-Haddad, Y., & Feuerstein, O. (2019). Killing mechanism of bacteria within multi-species biofilm by blue light. Journal of oral microbiology, 11(1), 1628577.