Pro-Oxidant Properties of Curcumin Induced by Light

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Curcumin, a natural polyphenol widely used as a spice, colorant and food additive, has been shown to have therapeutic effects against different disorders, mostly due to its anti-oxidant properties. However when used in excess and in the presence of light, curcumin can be toxic, because can generate reactive oxygen species (ROS), including singlet oxygen ($^1O_2$) and therefore act as a pro-oxidant.

curcumin singlet oxygen pro-oxidant photodynamic therapy light

1. Introduction

Curcumin (Cur) absorbs light in the UV-VIS range. An ethanolic solution of Cur shows three maxima at 220 nm, 262 nm and, in the VIS range, at 424 nm. The absorption of radiation by Cur molecules results in their transition to an excited singlet state, and, consequently, to an excited triplet state. Next, due to the energy transfer from an excited triplet state of Cur to molecular oxygen, singlet oxygen ($^1O_2$) is generated in a Type II photosensitized oxidation reaction. Type I, involving free radicals, seems to be less feasible in case of Cur [1]. As a result of $^1O_2$-induced oxidative stress, protein and lipid peroxidation occurs as illustrated in **Figure 1**.

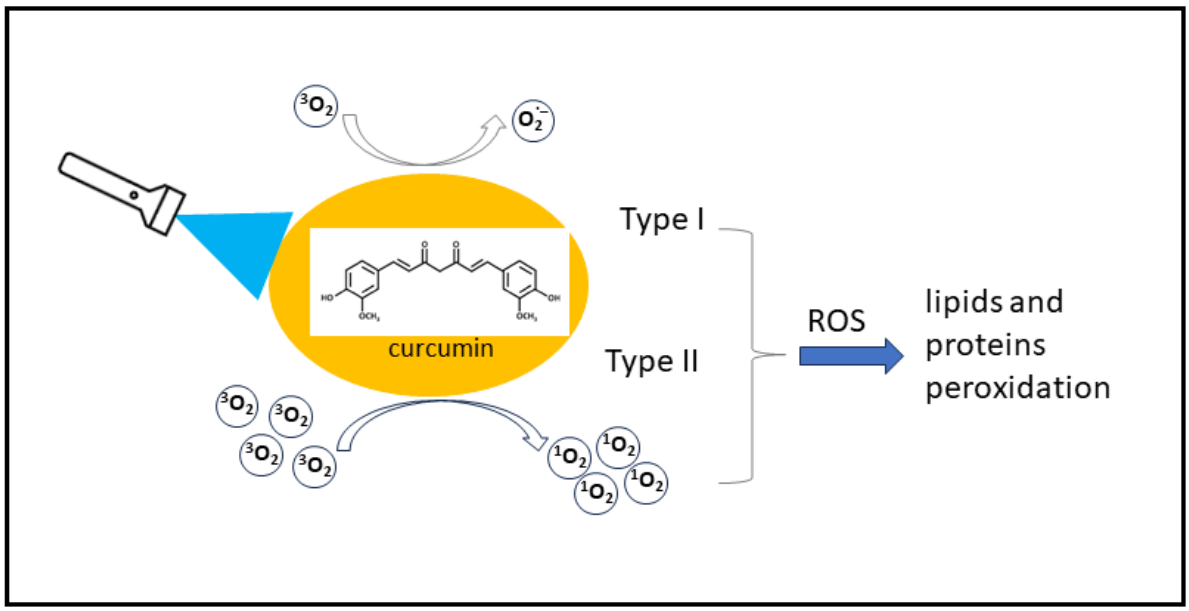

Figure 1. Scheme of mechanisms of curcumin induced photooxidation reactions. ROS- Reactive oxygen species, $^3O_2$ -molecular oxygen, $O_2^{\bullet-}$- superoxide anion, $^1O_2$ - singlet oxygen

2. Pro-Oxidant Properties of Curcumin Induced by Light

The recent studies have shown that Cur under blue light irradiation (438 nm) can generate $^1O_2$ not only in solvents, but also in liposomes, which have been used as a model of cell membranes [1]. In such systems, as well as in cells, $^1O_2$ generated by Cur can diffuse into both the lipid and aqueous phases and cause oxidation of the proteins and lipids present there. In particular, $^1O_2$ generated by Cur has been shown to be the main reactive oxygen species (ROS) responsible for cholesterol oxidation in liposomes and cells. The application of blue LED light (438 nm) in the presence of 10 μM Cur to HaCaT cells showed that the amount of $^1O_2$-specific 5α-OOH cholesterol hydroperoxides was 5.5 times higher than that of free radical-dependent 7α/β-OOH hydroperoxides [1]. The quantum yield of $^1O_2$ generation by Cur is estimated to be around 4% [1], which is not particularly high, especially when compared to a known photosensitiser such as Rose Bengal (76% [2]). However, due to the association and accumulation of Cur in membranes it may induce a photodynamic effect. For this reason, studies have been undertaken on possible curcumin's application in photodynamic therapy (PDT), as recently reviewed in [3][4].

PDT is based on the use of light of a specific wavelength and non-toxic photosensitizers causing a photodynamic effect in order to treat various skin diseases or tumors. The dual-specificity of PDT relies on accumulation of the photosensitizer in diseased tissue and also on localized light delivery [5]. Due to its hydrophobic nature, Cur accumulates readily and rapidly (less than one hour) in cell membrane [6][7] and in mitochondrial membranes, which was shown using confocal microscopy and fluorescence techniques [8]. Lipid and protein peroxidation was accompanied by a change in mitochondrial potential and decrease in metabolic activity of HaCaT cells, observed immediately after the end of cell irradiation, and also after 24 hours [1]. Presumably, depending on the Cur concentration used, necrosis or apoptosis takes place. However, while various concentrations (in micromolar range) of Cur are available and can be used i*n vitro,* its bioavailability remains low *in vivo*, limiting its potential use in PDT. Studies of Wozniak *et al*., [9] on melanoma (MugMel2), squamous cell carcinoma (SCC-25), and normal human keratinocytes (HaCaT) cell lines showed that possible PDT using Cur can be enhanced by using Cur encapsulated in hydrogenated soy phosphatidylcholine liposomes. Moreover, as a result of liposome curcumin-based photodynamic effect an increased ratio of apoptotic and necrotic cells was observed. The study clearly demonstrated that this form of Cur decreased malignant cell motility following the treatment. Interestingly, a minimal phototoxic reaction was observed in normal keratinocytes subjected to the same Cur dose [9]. Therefore, Cur lipophilicity, which becomes an obstacle in its direct delivery, can come handy in producing its different formulas such as liposomes. This would offer extended possibilities for controlled compound delivery. On the other hand, curcumin's modifications introduced to increase its bioavailability may lead to its accumulation in the skin, which can cause undesirable side effects upon exposure to light [3]. Another limitation of using Cur in PDT is low tissue penetration abilities of blue light. Because of that curcumin-based PDT may be effective only in treatment of superficial lesions or against microorganisms (bacteria, fungi) [3][10].

Resistance to conventional antimicrobial chemotherapy leads to search for alternative therapies such as PDT. Generally, PDT against microorganisms would not be effective in case of systemic infections but must be focused on the areas where it is relatively easy to apply light. Especially in case of Cur, which absorbs blue light of low tissue penetration abilities (0.3-2 mm) [11][12], this limitation has to be considered. However, blue light has high

energy, which absorbed by curcumin causes the generation of $^1O_2$, that can diffuse through a microorganism cell and damage different structures. Curcumin-based PDT against microorganisms makes sense, especially to combat drug-resistant biofilms, since their thickness ranges from 5 to 88 μm, through which even blue light penetrates. Oral candidiasis, which is the most common opportunistic infection caused by increased growth and penetration of fungal species such as *C. albicans, C. glabrata* and *C. tropicalis,* in oral tissues, can be treated with Cur combined with LED irradiation [13]. Carmello demonstrated the potential of curcumin-assisted photodynamic action to cause DNA damage in *C. albicans* [14]. Widespread candidiasis in immunocompromised patients can cause high mortality [15]. Treatment of *Candida spp*. infections is routinely based on the use of drugs, which can be topical or systemic [16]. However, the use of standard antifungal therapy may be limited due to its toxicity, low efficacy or resistance of microorganisms after prolonged exposure to the drug. Curcumin-based PDT is therefore a promising tool. Although most of the studies are done on bacteria and fungi cultures or biofilms, there are also examples of curcumin-based PDT in humans. Leite *et al.* [17] reported an *in vivo* curcumin application for oral decontamination (salivary microorganisms). Another example is the study performed by Paschoal *et al*. [18]. The authors reported an *in vivo* evaluation of antimicrobial and anti-inflammatory properties of Cur under light activation on the plaque accumulation and gingival bleeding in adolescents under fixed orthodontic treatment. To the best of our knowledge, there are no clinical data available involving curcumin-based PDT against cancer. Because most of the current research on Cur in combination with light is focused on *in vitro* experiments, and few on animal models, clinical studies are needed to prove its efficacy in PDT.

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