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Review Article

Structure-Function Elucidation of Antioxidative and Prooxidative Activities of the Polyphenolic Compound Curcumin

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Phenolic compounds have been very well known for their antioxidant properties, owing to their unique ability to act as free radical scavengers which, in turn, is an outstanding attribute of their unique biochemical structure. Recent accumulating lines of evidence inculcate sustainable interest and curiosity towards the chemoprotective nature of the natural polyphenolic compound curcumin (diferuloylmethane) against oxidative stress-mediated disorders. Curcumin is naturally found as a constituent of dietary spices called turmeric, extracted from the plant Curcuma longa. However, like every phenolic antioxidant, curcumin possesses a concentration and medium dependent anti- and pro-oxidant behaviour. A detailed study of the structure-function analysis and the understanding of the mode of action of curcumin as well as its chemical analogues is thus essential to understand the selective biochemical consequences of curcumin. Moreover, the presence of transition metal ions, route of administration, and localized tissue are also the vital decisive factors to determine curcumin behaviour. With this viewpoint, this paper sheds lights on the medium dependent prooxidative and antioxidative attributes of curcumin. Further, with respect to emergence of nanocarriers, a brief discussion focusing on the biochemical effect exertion of curcumin chiefly due to targeted and slow release has also been added towards the end.

1. Introduction

Phenolic compounds are widely accepted and recommended for their antioxidant activities [1–3]. The chemical structure of the phenolic compounds imparts them the ability to serve as free radical scavengers. A phenolic compound consists of a benzene ring and an alcoholic hydroxyl group, which are the defining features of its acidic nature. The type of the compound to be reduced, the degree of methoxylation, and the number of the hydroxyl groups present are some of the vital parameters that determine the antioxidant activity of a phenolic antioxidant. A diligent look into the structure of typical alcohol and a phenol leads to the conclusive finding that, in alcohols, the –OH group is bonded to saturated carbon atom while, in case of phenols, the hydroxyl (–OH) group is bonded to an unsaturated carbon atoms and this is clearly an indication that release of hydrogen ion is easier from the phenols than from the corresponding alcohols.

That's why phenols are widely known by the name carbolic acid. Furthermore, pK_a value for phenols is also more than that of the typical alcohols, which makes phenol a stronger acid than the alcohols [4].

A phenolic antioxidant has a characteristic hydroxyl group (–OH) attached to the benzene ring, in its structure. When reactive oxygen species (ROS) are present at a certain concentration, they influence the activity of electron releasing substituents present as substituents on the phenyl ring substituent in a phenolic antioxidant. As a result of this, the O–H bond is broken and the hydrogen ion is released. This hydrogen ion is made available to nucleophilic free radicals, which subsequently quenches their reactive tendencies. The rapidity, with which this happens, depends on the relative

stability of the formed oxidized product of the phenolic antioxidant involved. This further depends on the stability of the simultaneously generated phenoxide ion of the phenolic molecule, formed during the course of its antioxidant activity. The inherent delocalized large pi-electron density is another feature that contributes to the antioxidant potential of the phenols [4]. Thus, like other antioxidants, phenolic antioxidants can be classified as primary or chain breaking and secondary or preventive antioxidants. The primary phenolic antioxidants can be grouped into the categories of hydrogen atom transfer (HAT) and single electron transfer (SET) antioxidants. Phenolics are also considered to operate as secondary oxidants due to their ability to bind potentially with prooxidative metal ions [3].

Curcumin (diferuloylmethane) is polyphenolic compound derived from spices turmeric, a product of the plant curcuma longa [5]. The pigments responsible for yellow color of curcumin are phenolic in nature and are known by the name curcuminoids, which occur naturally in curcumin. Naturally occurring curcuminoids are a mixture of curcumin (77%), demethoxycurcumin, DMC (17%), and bisdemethoxycurcumin, BDMC (3%) [6, 7]. Figure 1 highlights the key potential benefits of curcumin with respect to its anticancer, antioxidative, anti-inflammatory, and immunemodulatory activities. Curcumin modulates several cell signaling pathways and therefore has been reported to possess pleiotropic activities [8, 9]. Several experimental and clinical studies have been, as well as, are currently being keenly pursued to understand the diverse immunoprotective effects of curcumin against various immunologically impaired pathophysiological conditions. One of the mechanisms through which curcumin exerts its therapeutic effects is through the antioxidative functioning. Curcumin is a very wellstudied and documented antioxidant which possesses phenolic hydroxyl groups as its active sites and is therefore termed as a phenolic antioxidant [10–13]. In an interesting study, K. C. Das and C. K. Das have explained the mechanistic scheme for understanding the chain of biochemical events through which curcumin quenches the reactive oxygen species (ROS) and brings about the subsequent reduction in free radical reacting capacities [14]. On the contrary, the proapoptotic activity of curcumin and its various derivatives on cancer cells is dependent on the generation of ROS [15]. Other reports also suggest that in cancer cells, curcumin or its methyl derivatives act as potential prooxidant molecules by generating ROS [16–18]. Interestingly enough, curcumin is likely to show prooxidative effects on the cells, when administered or delivered at a high concentration [19]. Thus, the effectiveness of this phenolic compound to act either as prooxidant or antioxidant depends on its cellular location involved, the presence of metal ions at the site of free radical generation [20], and the overall context specificity. A comparative study of the structure-function relationship of curcumin is, therefore, highly essential to understand the potent antioxidative or prooxidative effects of this molecule. The text ahead describes and discusses the antioxidative and prooxidative activities of this phenolic compound and its relative effect, *via* its delivery using nanocarriers.

2. Experimental Foundation to Show Antioxidant Potential of Curcumin

Literature is replete with numerous studies employing different cell lines and confirming the antioxidative and anti-inflammatory activities of curcumin. In one such study, it has been shown that in vascular endothelial cells, curcumin mediates its protective effect by inducing the expression of the enzyme heme oxygenase-1 (HO-1) [21]. Significantly enough, HO-1 is very well known for its antioxidant potential [22]. One investigation on curcumin in human myeloid leukemia cell line (U937) and human embryonic kidney cells (A293) reports that curcumin inhibits the translocation of proinflammatory and prooxidative transcription factors, namely, the nuclear factor kappa B (NF-κB) from cytoplasm to the nucleus [23]. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) have also been reported as potential targets of curcumin in gastrointestinal epithelial cells [24] and human colon cancer cells (HT-29) [25] respectively. Of note, COX-2 and i-NOS are the potential proinflammatory molecules.

Curcumin also showed its antioxidant activity in animal models. In mice peritoneal macrophages, curcumin decreased the level of ROS at a concentration of 10 mM [26]. This action may be due to its ability to scavenge superoxide anion radicals and hydroxyl radicals. Treatment of bacterial lipopolysaccharide (LPS) treated mice with curcumin (92 μg/kg administered intragastrically) reduced hepatic iNOS mRNA expression to an extent of 50–70% [27]. All of these experimental investigations of curcumin reveal that curcumin can significantly attenuate inflammation and oxidative stress.

3. Elucidation of the Phenolic Structure of Curcumin and Its Antioxidant Potential

Biochemically, curcumin is a bis-α, β-unsaturated β-diketone which exists in equilibrium with its enol tautomer [28] (Figure 2). Further, results of the NMR studies have also confirmed that curcumin exists in solution in the form of keto-enol tautomer [29]. The highest antioxidant activity in curcumin can be obtained when the phenolic hydroxyl group is sterically hindered by the introduction of two methyl groups at the ortho position of the benzene ring [12]. Therefore, the presence of two structural elements, namely, the β-diketone structure and the hydroxyl group at the ortho position in the aromatic ring, are the governing factors for the antioxidant potential of curcumin. Several phenolic and non-phenolic analogs of curcumin have been developed as well as studied to improve its antioxidant potential. It has been experimentally found that phenolic analogs of curcumin are generally better and stronger antioxidant agents [10, 11, 13]. In another significant attempt, Somparn et al. have explained the mechanism of antioxidant activities of curcumin and its close analogues, elaborating that it is the gradual diminishing strength of hydrogen bonding between the oxygen and hydrogen of the hydroxyl group possessed by curcumin by the combined effect of electron releasing

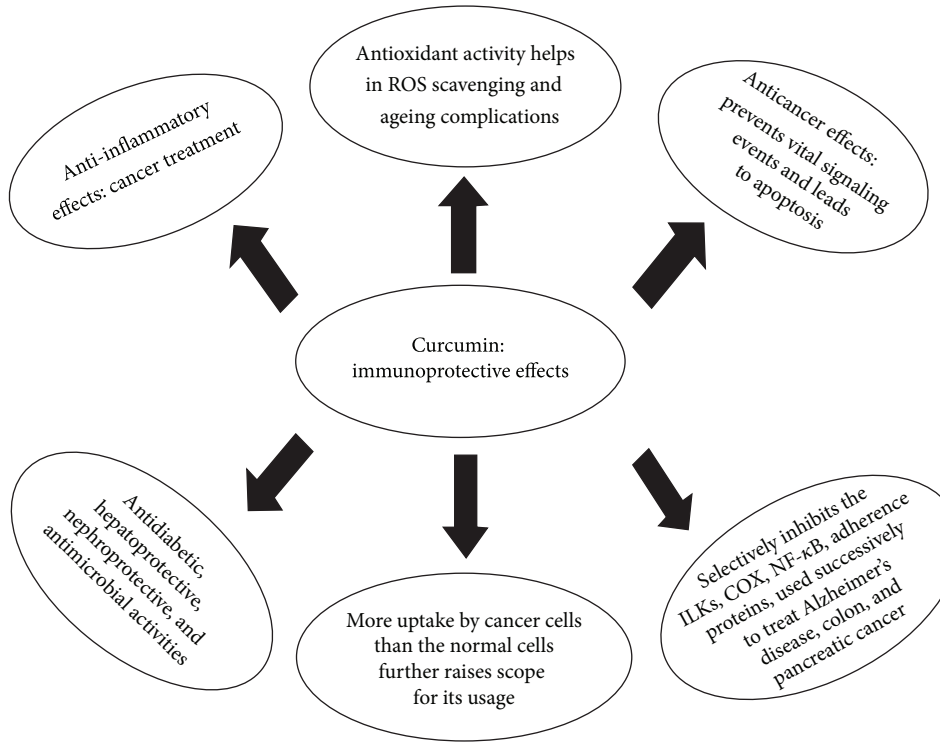

Figure 1: Established immunoprotective effects of curcumin, highlighting its immense potential and ability to serve antioxidant, anti-inflammatory, and anticancer effects. The protective effects of curcumin spanning large dimensions have been summarized.

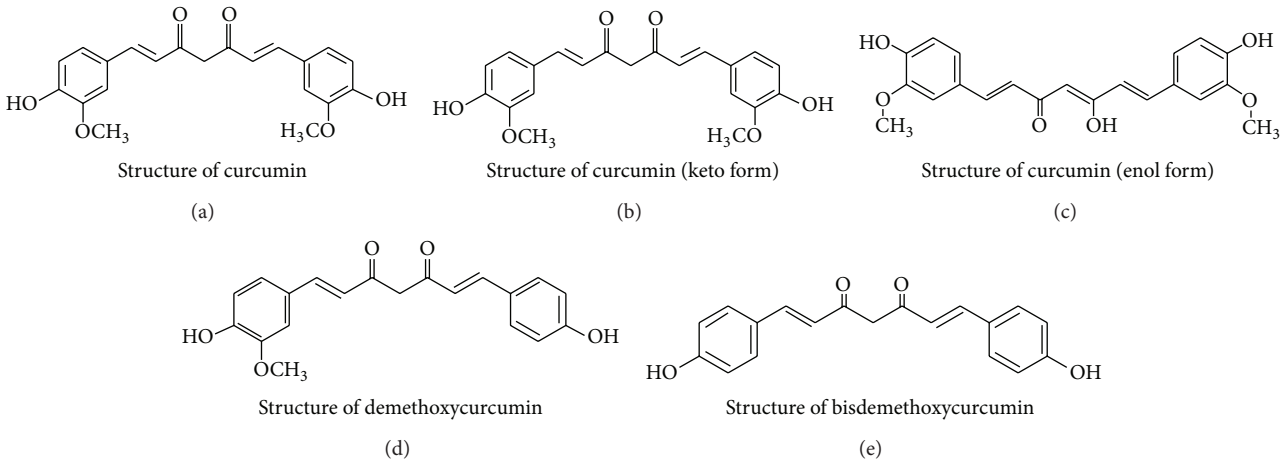

Figure 2: Structure of curcumin and its different analogs, depicting the chemical features of the main phenolic and nonphenolic analogs. The figure also highlights the keto and enolic forms of the curcumin, the most vital aspects as far as antioxidant potential is concerned.

methoxy group that it has on its benzene ring and their corresponding π-conjugation within the phenyl ring that is responsible for the release of H^+ ions from the curcumin and the corresponding quenching of free radicals generated. The authors have further argued that it is due to this that the antioxidant activity of curcumin is greater than that of the DMC [30]. Moreover, using this mechanism as hypothesis, one natural analogue of curcumin, namely, hexahydrocurcuminol discussed by Anand et al., can be utilized instead of curcumin as this has characteristic presence of four hydroxyl groups in its structure [7]. Not only this, in this contribution, but also the authors have significantly discussed the analogues that can be naturally or synthetically derived or obtained. Some of these analogues have been very rare in ther application, so studies can be optimized using these curcumin analogues to ameliorate the bioavailability related issues. In another comprehensive review article, Jurenka has reviewed the fundamental details of the preclinical and clinical research studies of curcumin, showing potent anti-inflammatory activity of curcumin [31].

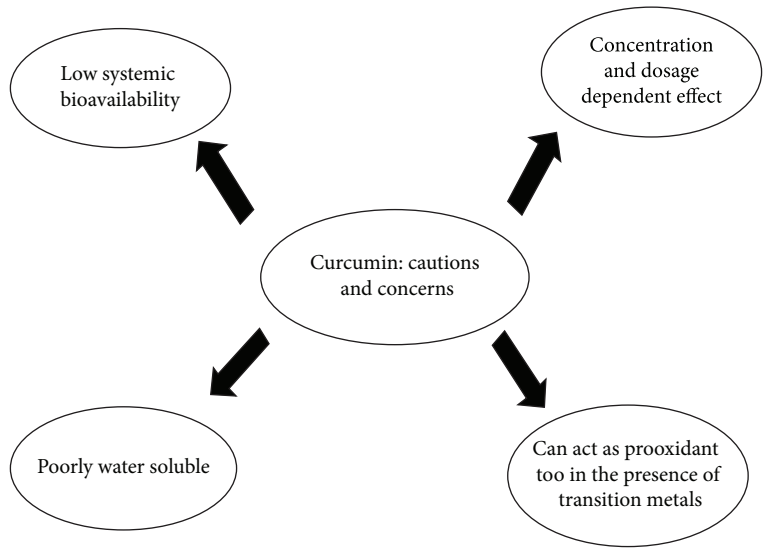

Figure 3: Crucial attributes of curcumin, highlighting its prooxidative activities and concentration dependent multifarious effects. Deleterious aspects with strong effects, depending on local conditions and concentration of the delivered antioxidant, have been pinpointed.

4. Factors Affecting Antioxidative Potential of Curcumin

The following factors affect the antioxidant potential of curcumin.

4.1. pH of the Localized Environment Determining the Antioxidant Potential of Curcumin. The antioxidant potential of curcumin depends not only on its structure but also on the pH of the localized micro-environment. At pH 3–7, curcumin acts as an extraordinarily potent H-atom donor. The quick release of H-ion from the curcumin is very much beneficial for its antioxidant action. The release of the H-atom from the hydroxyl group of the curcumin molecule is directly correlated with the quenching of free radicals and subsequent ROS species involved. This is because, in the keto form of curcumin, the heptadienone linkage between the two methoxyphenol rings contains a highly activated carbon atom and the C–H bonds on this carbon are very weak due to delocalization of the unpaired electrons of the adjacent oxygen atoms. In contrast, at all pHs above 8, the enolate form of the heptadienone chain predominates and curcumin acts mainly as an electron donor, a mechanism more typical for the scavenging activity of phenolic antioxidants [12]. Moreover, the antioxidant activity of curcumin can be increased by making certain alterations in its native structure which can possibly make it an electron rich molecule so that it can act as a better reducing agent in order to reduce the concentration of ROS molecules and make the corresponding phenoxide ion more stable, which chemically favors the exertion of its antioxidant activity [32]. One interesting method involving the structural alteration of curcumin native structure can be to increase the length of the hydrophobic alkoxy group attached to the benzene ring in the structure of curcumin as this will make the ring more electron rich and through which, the weakening of O–H bonds at the phenyl ring would be more pronounced to get broken and that would ultimately enable an easier and quicker H-ion release. As an instance, we can substitute ethoxy and higher alkoxy groups with the native methoxy groups present as phenyl ring substituents.

4.2. Concentration of Curcumin Determining Its Antioxidative or Prooxidative Activities. Reports by Chen et al. suggest that curcumin quenches ROS production at low concentrations and induces ROS production at high concentrations [33]. A recent report by Huanga et al. confirms that curcumin, in a concentration-dependent manner, plays both antioxidative and prooxidative roles in primary neuron tissues treated with Cu^{+2} [34]. Another significant study by Banerjee et al. shows that the prooxidative activity of curcumin depends on its dosage and the corresponding prevailing chemical conditions in the vicinity. While at low concentrations, curcumin shows antioxidative activity, at higher concentrations, it shows prooxidative activity [19]. Studies using absorption and fluorescence spectroscopic methods show that cellular uptake levels of curcumin are higher in tumor cells than in normal cells [16]. Further studies show that low concentrations of curcumin may protect the hepatocytes by reducing lipid peroxidation and cytochrome *c* release. Conversely, higher concentrations provoke reduced glutathione (GSH) depletion, caspase-3 activation, and hepatocytotoxicity [35]. Interestingly enough, the tripeptide GSH is the most abundant antioxidant involved in human cells. The GSH levels in tumor cells tend to be lower than those of the normal cells, thus enhancing the sensitivity of tumor cells towards curcumin [18]. Interestingly, most of the tumor cells, but not normal cells, express constitutively active NF-κB and mediate their survival [32]. Curiously enough, NF-κB is a proinflammatory and prooxidative transcription factor. Curcumin can suppress the survival and proliferation of tumor cells by suppressing NF-κB-regulated gene products [36]. These studies led us to the conclusion that a high

concentration of curcumin is essential to show its prooxidant activity.

5. Prooxidant Abilities of Curcumin

5.1. Experimental Foundation to Show Prooxidative Potential of Curcumin. Like every phenolic antioxidant, curcumin imparts the resistance against free radical mediated stress in some circumstances by quenching ROS generation [14, 15] and promotes free radical generation under some other conditions [17, 18, 37]. Studies with various cell lines have also confirmed that curcumin possesses prooxidative activities. Curcumin-induced, Akt-mediated apoptosis of Caki renal cells was partially inhibited by cotreatment with *N*-acetylcysteine (NAC), which suggests the involvement of concomitant oxidative stress [38]. Interestingly enough, NAC is a potential antioxidant. It is further speculated that high concentrations of ROS generated by curcumin inside the cancer cells lead to apoptosis [39]. To understand the mechanism of curcumin induced cellular apoptosis, Kunwar et al. showed that, in cancer cells, methylation of the phenolic-OH group of curcumin decreases the antioxidant activity marginally and enhances the prooxidant activity, thereby making it a promising antitumor agent. This study showed that demethoxycurcumin (DMC) is a promising as well as more provident molecule that generated ROS in the tumor cells. Both curcumin and DMC were nontoxic to the lymphocytes, while exhibiting comparable cytotoxicity to the tumor cells [16].

5.2. Structural Elucidation of Prooxidative Potential of Curcumin. A number of studies have shown the specific structural moieties that mediate prooxidative action of curcumin. In one of these attempts, Ahsan et al. have shown that both prooxidative and antioxidative effects of curcumin are determined by the same structural moieties of the curcuminoids [40]. The finding that tetrahydrocurcumin is unable to produce ROS suggests the exclusive role of α,β-unsaturated carbonyl moiety of curcumin, to be responsible for the production of ROS [14]. Other studies have shown that the prooxidative action of curcumin can be related to the conjugated β-diketone structure of this compound [17].

A very interesting contribution to the illustration of enhanced prooxidative, antiproliferative, and anti-inflammatory effects of curcumin has been put forward by Ravindran et al., who have highlighted that some particular chemical modifications in the native structure of curcumin to the formation of its analogues result in the altered biological activities of curcumin. The authors of this study have compared the anti-inflammatory and antioxidant activities of curcumin, bisdemethoxycurcumin, and their structurally related chemical analogues by incorporating different substituent at various locations in the structure of the native compound. The scientists involved in this study attempted to vary the hydroxyl, methoxy, and phenyl group positions, through which they found out that the anti-inflammatory activity of bisdemethylcurcumin (BDC) is far better and much more than that of curcumin and it was also shown that BDC has the better ability to arrest the TNF-induced NF-κB activation. The contributors of this interesting biochemical study found that substitution of a methoxy group by a hydroxyl group at the metaposition of the phenyl rings in the structure of curcumin leads to an enhanced anti-inflammatory activity of the curcumin. This surprisingly increased anti-inflammatory activity of BDC can be due to its increased prooxidative behavior as established by previous studies. In a similar manner, the authors also found that, following the replacement of phenyl ring at the seventh carbon of heptadiene backbone by the hydroxyl group, a sharp increase in the antiproliferative activity of curcumin was observed [41].

Prooxidative activity of curcumin may be mediated through its interaction with redox regulating molecules of the cells. In this context, Fang et al. have shown that curcumin irreversibly inactivates thioredoxin reductase by alkylating a critical cysteine residue prevalent as a core location in the catalytic site of the enzyme [42]. This enzyme catalyzes NADPH-dependent reduction of thioredoxins, which play an important role in the substrate reduction and the subsequent development of defense against oxidative stress, thereby playing an urgent role in redox regulation. Another report showed that curcumin also inhibits interleukin-1 receptor-associated kinase (IRAK) through the modification of the protein's cysteinyl sulfhydryl groups *in vivo* [43]. Moreover, reducing glutathione (GSH), the highly abundant antioxidant of the cells has been shown to suppress curcumin-induced ROS production [14]. Quenchers of hydroxyl radicals, however, were ineffective in inhibiting curcumin mediated NF-κB suppression. Further, NAC partially reversed the effect of curcumin. Based on these results, it was strongly emphasized, in one of the compiled reports, that curcumin mediates its apoptotic and anti-inflammatory activities through the modulation of the redox status of the cell [44]. Metabolism of the polyphenolic rings of curcumin by peroxidases leads to generation of prooxidant phenoxyl radicals which, in some cases, are reactive enough to cooxidize GSH or NADH, a biochemical event that is accompanied by extensive oxygen uptake and the subsequent ROS generation [39].

5.3. Transition Metal Mediated Prooxidant Activity of Curcumin. In one of the much unexpected twists, it has been reported that prooxidative activity of curcumin is particularly critical and sharp in the presence of transition metal ions like those of iron and copper [20]. Curcumin binds with Cu^{+2} at three distinct sites. Two of the sites are provided by the phenolic and methoxy groups on the two benzene rings and the third site is due to the presence of 1, 3-diketone system between the rings. Binding Cu^{+2} with curcumin leads to the generation of ROS and enhancement in oxidative stress [40]. The chemical action of Cu^{+2} tagged curcumin on calf and plasmid DNA has reportedly been studied and, surprisingly, it resulted in the incision of the DNA molecule and it has been further verified through flow cytometry that this is due to the action of hydroxyl group of Cu^{+2} linked curcumin on the DNA molecule [45]. In a very interesting related study reported this year only, Leung et al. have very excellently

summarized exciting findings under which curcumin shows the antioxidant and prooxidant behavior. They have postulated that the anti-inflammatory and anticancer effects of curcumin are exerted through its interactive expression in the presence of transition metals such as those of zinc, copper, and iron in the corresponding damaged tissues or other *in vivo* locations. Interestingly, the contributors of this study have observed that when curcumin acts in the presence of copper ions in divalent stage (Cu^{+2}), it acts as a prooxidant and this ability mediates its anticancer effect through which curcumin acts as an anticancer agent and can result in the apoptosis of cancer cells *via* its elevated secretion of ROS molecules as well as the impact on key signaling events occurring in these cancer cells [46].

6. Nanotechnological Interventions to Enhance Bioavailability of Curcumin

Interestingly enough, a number of studies have suggested that curcumin suffers from very low systemic bioavailability and gets rapidly eliminated from the body tissues, mainly from liver and small intestines [47, 48] (Figure 3). Even though FDA investigations through rat model studies have established that an intake of curcumin to a limit of 12 g/day is safe for health, still this problem is acute as most of the curcumin goes through the body as such with very less effective usage. The problem appeared further multifold when some persons, with high dosage of administered curcumin, suffered from nausea, vomiting, stomach problems like diarrhea, and many others.

In this dimension, nanoscience and nanotechnology opens a very exciting window of opportunity via enabling the enhanced curcumin delivery through nanoscale carriers, carrying far lesser amount of the drug and promising a slow, targeted and gradual release. The delivery of curcumin through various nanocarriers including nanoparticles, nanoemulsions, nanosuspensions, nanofibers and many others has enabled a great deal of improvement in its systemic localized availability and the corresponding increase or amplification of its therapeutic and protective effects [49–52]. Studies have reported the enhanced benefits of curcumin delivered through nanoroutes to the extents of even 27 times [53]. One particular study presents a deep insight of thinking as it has proved that curcumin in the form of biodegradable nanoparticles of polycaprolactone is better absorbed and assimilated by the cellular organs. However, there are also some grave concerns associated with this strategy. For instance, the used nanocarriers can also initiate or elicit a toxic response if they are not engineered to be biocompatible and sometimes the particular drug-nanocarrier interaction can be disadvantageous. One crucial point of discussion about the delivery of curcumin with nanocarriers is that, with the use of nanocarriers, it remains available in the cellular locations to longer extents and this is responsible for its transition from being an antioxidant to a prooxidant. Interestingly, one particular 2010 review article highlights these kinds of permutation and combinations through an elaborate and exhaustive discussion on most of the antioxidants and the effect of their nanocarriers mediated delivery [54]. One exciting consequence that comes into mind after going through extraordinary anticancer potential of curcumin is that reports suggest that curcumin exerts its anticancer effects through the generation of ROS and signaling activities that lead to apoptotic genes getting activated in cancer cells. In this respect, it still remains to be seen how curcumin is able to do this and what if nanocarriers prolong its persistence to extend the duration of these impacts. The turning point question emerging out from this advancement is that how effectively curcumin is able to mediate its protective effect for the elimination of infected cells and whether the normal cells are also at risk from its prolonged antioxidant activity. These questions highlight an extremely likelihood possibility that curcumin might be exerting the anticancer effects through its prooxidant nature. Thus, it is still an intriguing area of concern, to know precisely, about the biochemical conditions responsible for antioxidant or prooxidative behavior of curcumin.

7. Conclusion

Phenolic antioxidants are thus, very essential biomolecules, to effectively control the alleviated levels of oxidative stress. In this reference, curcumin deserves special mention because of its natural origin, aesthetic belief, and the frequency of its routine usage since decades. The crucial factors affecting the use of curcumin as an antioxidant include its poor aqueous stability, systemic low bioavailability, and nonspecific deliveries in some instances; emanating primarily due to the intended route of delivery. However, beyond a particular amount also, its intake is deleterious for humans as well as other similar organisms. The most interesting aspect of these antioxidants is that they differ in their mode of ROS scavenging potential. Moreover, their antioxidative activity is different at various locations in the body. The need of curcumin might be different in different individuals, specifically depending on age, sex, and genetic makeup. Several intricate and extrinsic factors regulate the metabolism of curcumin. Curcumin can also exert prooxidative effects due to a varied number of reasons, including modification of its structure, concentration of curcumin, presence of metal ions, localized microenvironment inside different tissues, and overall redox status of the concerned tissues. Curcumin dependent prooxidative activity may be one the important reasons for the apoptosis of cancer cells. A detailed understanding of the structure-function relationship of curcumin will help to synthesize better analogs to eradicate a number of diseases and it will also be helpful to confront the increasingly challenging aspect of low systemic bioavailability.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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