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POWER AND MAGIC IN CURCUMIN & SELENIUM

Ruchika Chauhan[1], Madhu Chauhan[2*], Dharmesh Sharma[3]

1. Department of Biotechnology, Manav Bharti University, Solan, H.P.
2 Department of Chemistry, Manav Bharti University, Solan, H.P.
3 Department of Pharmacology, Himachal Dental College, Sunder Nagar, H.P.

ABSTRACT

The xenobiotic compound produces huge amount of reactive oxygen species and reactive nitrogen species which cause oxidative stress. In this review, we have explored the potential of selenium and curcumin protection against diseases that are caused by reactive oxygen species and reactive nitrogen species.

Key words: Curcumin & Selenium

INTRODUCTION

Free radicals are being formed during normal cellular metabolism and they are known to bestow to healthy functions in human health and development when they are not in surplus. Formation of free radicals is not limited to normal cellular process but also occurs upon exposure to certain chemicals (polycyclic aromatic hydrocarbon, chlorinated hydrocarbon etc.), radiation, cigarette smoke, and high fat diet. Exposure of a healthy cell to free radicals such as super-oxide, hydroxyl and Nitric oxide radicals is known to damage structures and consequently interfere with functions of enzymes and critical macromolecule. Mammalian cells possess detailed defense mechanism to detoxify free radicals. For normal cellular function, balance between formation of free radicals and their detoxification is essential. Disruption in such a balance is a

*Corresponding Author Email: mdhuchauhan@gmail.com

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result of excessive generation of damaging species or low levels of antioxidants due to this a cell enters a state of oxidative stress and is damaged. If the damage continues to exist the cell will enter a state of genetic instability that can lead to chronic diseases including cancer [1]. In both cytotoxicity and genotoxicity for initiation and promotion of multi-step carcinogenesis reactive oxygen species (ROS) and reactive nitrogen species (RNS) are found to be involved. They can cause DNA damage, activate procarcinogens, initiate lipid peroxidation, inactivate enzyme systems and change the cellular antioxidant defense system [2].

Chemoprevention is a new buzz word in cancer prevention which involves the use of drugs to lower the risk of cancer. Cancer is taking over heart diseases as the number one killer in developed countries. 25% of all deaths in the United States are due to cancer. Chemoprevention has emerged as a new and exciting weapon in the fight against cancer. By definition, chemoprevention is the use of drug to prevent a disease from occurring. Ideally, a chemo preventive agent helps the body to recognize mutated cells and get rid of them from the system before they grow and divide uncontrollably [3].

Presently, approximately 400 compounds are being studied as potential chemopreventive agents, mainly in laboratory research. Over 40 of these compounds are being studied in clinical trials. Some of these agents are being investigated as single agents; others are being tested in combinations of two drugs. Chemoprevention trials look at possible ways to prevent cancer with interventions that include drugs, vitamins, diet, hormone therapy, or other agents. Some classes of chemopreventive agents have shown hope in clinical trials and are believed priority substances for study. These agents include Anti-Androgens, Carotenoids, Curcumin, Indols, isothiocyanates, NSAIDS, ornithine decarboxylase inhibitor, Polyphenols, PPAR gamma agonist, Retinoids, Rexanoids, Selective Estrogen Receptor Modulators, Selenium compounds, Statins, Sulfur containing Antioxidants, Vitamin D analogs. An effective chemopreventive agent will not in any case going to alter quality of life, and is ideally inexpensive, safe, well tolerated, and effective in preventing more than one cancer. While patients at risk of return of cancer but are currently tumor-free take part in chemoprevention studies, some actually may be receiving treatment as opposed to prevention. Carcinogenesis can be regarded as an assemblage of genetic or biochemical cell damage, which offers a variety of objectives for chemopreventive agents to prevent or inhibit the slow progression from early genetic lesions to tumor development. Modulation of drug metabolism, anti-oxidant, radical-scavenging, anti-inflammatory, anti-tumor

promoting and anti-proliferative activities as well as induction of terminal cell differentiation and apoptosis includes well established molecular mechanisms of chemoprevention[4-5].

CURCUMIN

Curcumin is commonly called diferuloyl methane. It is a hydrophobic polyphenol derived from the rhizome (turmeric) of the herb Curcuma longa. Because of wide spectrum of pharmacological activities of turmeric it has been used traditionally for many ailments. Curcumin has been keyed out as the active percept of turmeric, chemically, it is a bis-a, b-unsaturated b-di ketone that exhibits keto-enol tautomerism. Curcumin has been shown to exhibit antioxidant, anti inflammatory, antimicrobial, and anticarcinogenic activities. It also has hepatoprotective and nephroprotective activities, inhibits thrombosis, defends against myocardial infarction, and has hypoglycemic and antirheumatic properties. Moreover, curcumin has been shown highly safe even at very high doses in various animal models and human studies. In spite of its efficaciousness and safety, curcumin has not yet been Okayed as a curative agent. The poor aqueous solubility, relatively low bioavailability, and intense staining color of curcumin have been fore grounded as major troubles, and accordingly search for a ‘‘super curcumin’’ without these problems and with efficacy equal to or better than that of curcumin is currently happening[6].

Targets of Curcumin

Numerous molecular objectives for curcumin have been discovered over the years. These targets fall into two categories, namely, a target to which curcumin directly binds and regulates their activity and those of which modulation of activity is collateral or secondary. The targets with which curcumin directly interacts include cyclooxygenase (COX)-2, lipoxygenase (LOX), glycogen synthase kinase (GSK)-3b, phosphorylase-3kinase, xanthineoxidase, N-aminopeptidase, amyloid protein, human a1-acid glycoprotein, autophosphorylation activated protein kinase, DNA polymerase, focal adhesion kinase (FAK), glutathione, albumin, P glycoprotein, pp60 src tyrosine kinase, thioredoxin reductase (TrxR), tubulin, topoisomerase II, ubiquitin isopeptidase and toll- like receptor (TLR)4. The binding constant of curcumin to these targets starts at nano molar levels, as in GSK3b, 5-LOX, b amyloid and TLR4, and advances to micro molar levels in glutathione S-transferase (GST), TrxR, DNA polymerase- l and tubulin. Curcumin has also been shown to bind certain divalent metal ions such as Fe, Cu, VO2+, Mn and Zn. Curcumin has high affinity for Fe and Cu with dissociation constants of approximately 3 mM for each. The metal binding is mediated through the ketone group of curcumin. The

molecular targets indirectly affected by curcumin might be up regulated or down regulated depending on the particular target. Curcumin has been shown to activate various transcription factors including peroxisome proliferator-activated receptor-g (PPAR-g), p53, NF-E2-related factor (Nrf2), C/EBP homologous protein (CHOP) and activating transcription factor 3 (ATF3). The activated PPAR-g has been show to mediate the suppression of expression of cyclin D1 gene and epidermal growth factor receptor (EGFR) genes. Induction of p53 mediates the expression of cell-cycle-dependent kinase inhibitor p21 and Nrf2 activation by curcumin has been associated with induction of GST and NADP (H) quinone oxidoreductase (NQO) and hemeoxygenase-1. Curcumin is also known to induce the expression of death receptor 5 (DR5), glutathione reductase, transferrin receptor 1, iron regulatory protein and ferritin H and L through a mechanism that is not fully interpreted. Curcumin has been also shown to down regulate various transcription factors (e.g. nuclear factor [NF]-kB, hypoxia inducible factor [HIF]-1a, activator protein [AP]-1, signal transducers and activators of transcription protein [STAT]-3, specificity protein [SP]-1 and b-catenin), protein kinases (e.g. protein kinase [PK]A, PKC, Src, FAK), growth factor receptors (e.g. EGFR and human epidermal growth factor receptor 2 [HER2; also known as p185 neu and ErbB2]), chemokines (e.g. chemokine ligand [CXCL]1 and CXCL2), chemokine receptore.g. CXCR4), antiapoptotic proteins (e.g. cellular FLICE like inhibitory protein [cFLIP], inhibitor of apoptosis protein [IAP], X-linked IAP [XIAP], Bcl-2 and Bcl-xL), cell-cycle regulatory proteins (e.g. cyclin D1, cyclin E and c-myc), invasion and angiogenesis biomarkers (e.g. matrix metalloproteinase [MMP]-9, vascular endothelial growth factor [VEGF] and urokinase plasminogen activator [uPA]) and inflammatory biomarkers (e.g. tumor necrosis factor [TNF], interleukin [IL]-1, IL-6, COX-2, 5-LOX, prostate specific antigen [PSA] and C-reactive protein [CRP]). In addition, curcumin is a potent inhibitor of the activity of constitutive photomorphogenic 9 (COP9) signalosome-associated kinase and p300/cAMP-response element binding protein (CREB) [8], an acetyl transferase that can regulate the expression of many genes. Based on these objectives, it can be seen how curcumin could regulate anti-inflammatory, antiproliferative and pro-apoptotic activities. Curcumin has been shown to inhibit the development and endurance of almost all types of tumor cells analyzed up to now. Down regulation of AP-1, cyclin D1 and cyclin E and up regulation of p21, p27 and p53 have been related with the antiproliferative effects of curcumin [7, 8, 9].

Facts about Curcumin

Although curcumin has been shown to regulate various objectives that have been associated with cancer and several other chronic diseases, one of the most important limitations with curcumin is its bioavailability. Whether carried out in animals or human, examines have shown that when administered orally, curcumin is poorly bioavailable. Either no curcumin at all was found or only low levels of curcumin metabolites were discovered in the serum or in the tissue. Curcumin seems to be metabolized through conjugation and reduction. Orally administered curcumin undergoes conjugation leading to the formation of curcumin glucuronide and sulfates in the intestine and in the liver. Curcumin given systemically undergoes reduction leading to the formation of tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin. Conjugation or reduction metabolites of curcumin have been found to be biologically inactive. The low bioavailability of curcumin is due to the hydrophobic nature of the molecule. Various approaches have been undertaken to raise the bioavailability. These approaches involve (i) the use of adjuvants such as piperine that intervene with glucuronidation, (ii) the use of liposomal curcumin, (iii) curcumin nanoparticles, (iv) the use of curcumin phospholipid complex and (v) the use of structural analogs of curcumin [10, 11, 12].

SELENIUM

Selenium is a significant element from environmental and biological point of view being necessary in a very narrow concentration range, while outside this range deficiency or toxicity occurs. It has been accepted as an integral component of different enzymes such as glutathione peroxidase and thioredoxinreductase, which take part in the antioxidant protection of cells. Several studies have proposed that some organic forms of selenium could show anticarcinogenic properties against certain types of cancer. It has been recommended on the basis of this estimate, that daily selenium intakes for humans change according to the country or region, age and sex [13].

Targets of Selenium

Selenium to the great degree is regarded as a protective agent against cancer risks. Supranutritional levels of selenium have benefits in preventing several types of cancer, which includes lung cancer, colorectal cancer, and prostate cancer. The chemopreventive role of selenium is well supported by epidemiological, preclinical, and clinical evidence. In addition, there is much evidence indicating the potential of selenium compounds in cancer chemotherapy. Among the suggested anti-cancer mechanisms, cell growth inhibition and apoptosis were contended to be critical. Former work, depicted that selenite sets off stress-related signaling

pathways, including JNK and ERK, leading to an apoptotic cascade. Selenite, when dispersed into the cytoplasm, could disturb the intracellular redox status by reacting with intracellular thiols. In the presence of thioredoxin reductase or the thiol group, it is reduced into selenide, which cycles incessantly to give ROS in the presence of thiols and O_2. Indeed, the disturbance of the redox system and later ROS generation were determined to be causally associated to cancer cell death induced by selenite.The exact mechanisms by which selenium activates the apoptotic machinery still remain poorly understood. Bcl-2 family proteins play a leading role in the regulation of cytochrome-C release and apoptosis. This family includes antiapototic proteins such as Bcl-2 and Bcl-xL and "multidomain" proapoptotic proteins such as Bax and Bak. Bax is found in the cytosol despite of the presence of transmembrane domain, where it maintains in an inactive form. In response to apoptotic signals, Bax alters its conformation, exposing its C-terminal membrane-anchoring domain and inserting into mitochondrial membranes. Oligomerization of Bax or Bak at the mitochondrial membrane level regulates the emission of cytochrome c and other apoptogenic proteins into the cytosol. Cells deficient in Bax are predominately resistant to apoptosis induced by a number of death stimuli and plays a critical role in apoptosis regulation. Bax is activated and transferred to the mitochondria by selenite. Selenite induces the oxidative stress response and an increase in intracellular ROS levels. Therefore used as a chemopreventive agent [14-15].

Facts about Selenium

The main function of Selenium (Se) compounds is to regulate important protein and many cell functions, including enzyme catalysis and signal transduction. Selenium compounds show anti-inflammatory, anti-oxidation, anti-cancer, and anti-HIV activities in animal and human studies. Micro molar amounts of serenity, an inorganic form of selenium, suppress the growth and induce apoptosis in human colonic carcinoma cells, brain tumor cells, and breast cancer cells. Serenity also has potent anti-inflammatory properties and was previously shown to inhibit DNA binding by transcription factors AP1, TFIIIA (transcription factor IIIA), and Sp1. Inhibition of transcription factors and downstream growth regulatory pathways is hypothesized to be a major mechanism for the anti-inflammatory and anti-cancer effects of selenium compounds. The general hypothesis for mechanisms of action of serenity is through reactions with specific cytokine thinly groups in proteins [16-17].

Selenium has so many anti-cancer actions that it is hard to establish which ones are predominant. Selenium affects oxidative stress, DNA methylation, DNA repair, inflammation, apoptosis, cell proliferation, carcinogen metabolism, hormone production, angiogenesis and immune function[18]. Selenium compounds are also considered as "Janus compounds", i.e., products with a double face, because of their contrasting behavior that is concentration dependent. Selenium has beneficial effects at low doses, whereas high doses are toxic and possibly carcinogenic. The threshold concentration has not yet been established for these opposing activities [19].

CONCLUSION

Herbal remedies such as Curcumin and selenium have many sanatory attributes against many diseases. Our challenge in the modern age is to scientifically unravel the many claims and conflicts about these herbal remedies. More research is necessitated to make them available for everyone in variety of products.

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