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Quranic Verse No. 8 of Surat Al-Jumu'ah Leads us to Describe Cancer and Determine Its True Cause (Part-III)

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Abstract

Therapeutic strategies for destroying cancer cells by making its death programs run again. The normal cell passes through several stages (Accumulation stage, Detoxification stage, Formation of free radical stage and Activation of nuclear factor kappa B stage and the shutting down of programs of cell death stage) to become a cancerous cell. The success of the therapeutic strategy to treat cancer depends on making either one or both programs of cell death run again. Shutting down one stage completely will be sufficient to stop the transformation of the natural cell into a cancerous cell, which eliminates the production of hydrogen peroxide, thus the activity of the NF-Kb will be inhibited. However, shutting down all stages is the most comprehensive therapeutic strategy and guarantees treatment success.

Keywords

Cancer, Therapeutic Strategy, Accumulation, Detoxification Enzymes, Free Radicals, Antioxidants, H_2O_2, Glutathione, NF-Kb, Sulforaphane, Flavonoid, Cur Cumin

1. Introduction

Cancer is a very serious disease that kills more than 8 million people a year. Cancer is difficult to treat and all treatments so far cannot save the lives of all patients. Cancer is the cell fleeing from death. A normal cell passes through a several stages to convert to a cancerous cell.

To prevent this, we must follow those stages, starting from the entry of the

harmful substances into the cell or its exposure to radiation until the shutdown of the intrinsic and extrinsic programs of cell death. This is planned as follows:

1) Studying the nature of harmful substances and why they accumulate inside the cell.

2) Studying how to remove these harmful substances from cells.

3) Studying the effect of these harmful substances or radiation on the cell.

4) Studying the types of free radicals generated and its relation to the nuclear factor kappa B.

5) Studying how the NF-Kb is activated and how it shuts down the intrinsic and extrinsic programs of cell death.

2. Material and Methods

Cancer is a phenomenon where the cell flees from death [1]. In order for the cell to flee from death, it must pass through several successive stages (Accumulation stage, Detoxification stage, Formation of free radical stage and Activation of nuclear factor kappa B stage) ending with the complete shutdown of the pathway of both the intrinsic and extrinsic programs of cell death.

2.1. Stage-1: Accumulation of Harmful Substances in Cells

The movement of harmful substance molecules in or out of the cell depends on the polarity of these molecules and is divided into polar and nonpolar molecules.

Polar molecules (hydrophilic molecules) = love water and nonpolar molecules (hydrophobic molecules) = hate water.

The polarity of the cell is controlled by the nature of the internal surface of the cell membrane which is facing the cytoplasm, as well as the nature of the harmful substance molecules.

The cell membrane consists of two layers of phospholipids each layer composed of a lipid and phosphate group. The Phosphate group, (hydrophilic) is facing the cytoplasm. This property expels the lipid molecules (hydrophobic) away from it from all directions (the power of dissonance is equal from all directions) so, the hydrophobic molecules keep away from internal surface and remain in the middle of the cell, called a non-polarity molecules.

Since, cellular membranes are primarily lipid based, the lipid soluble substances can freely pass through the cell membrane into the cell but are much more difficult to remove (2) so the hydrophobic molecules accumulate. The cells get rid of these molecules by detoxification system.

2.2. Stage-2: Detoxification

Detoxification is the metabolic process of removing unwanted lipid-soluble compounds from the body and its reactions occur throughout the body. Detoxification reactions follow three steps or (phases). The process is performed by three sets of cellular proteins or enzymes, called phase I (transformation) enzymes and phase II (conjugation) enzymes, phase III (transport) proteins [2].

2.2.1. Phase-I Detoxification Enzymes

Phase I enzymes begin the detoxification process by chemically transforming lipid-soluble compounds to water-soluble compounds in preparation for phase II. The bulk of the phase-I reactions is performed by a family of enzymes called the cytochrome P450. Accumulation of harmful substances leads to high levels of phase-I detoxification enzymes to metabolize them. Each molecule of the harmful substances needs one molecule of phase-I detoxification enzyme to metabolize it, which results in the generation of one molecule of free radical [3]. The chemical analysis of cancer cells showed exaggerated enzymatic activity as follows:

1) Cytochrome P450 (CYP) 1B1

Cytochrome P450 (CYP) 1B1 is over expressed in tumor cells. It performs the bulk of phase-I reactions and serves as a source of superoxide anion and H_2O_2. Both may convert to highly reactive hydroxyl radical (OH) by iron (Fe^{2+})-catalyzed [4] [5].

2) Flavin mono-oxygenase enzyme

Flavin mono-oxygenase enzyme (FMOs) has been associated with cancer. Flavin mono oxygenase (FMOs) and Cytochromes P450 are important in the process of non-nutrition foreign compounds metabolism. They add molecular oxygen to lipophilic compound making them more water-soluble to ensure rapid excretion [6].

3) Xanthine oxidase enzymes

Xanthine oxidase enzyme (XO) is recognized in high levels in human brain tumor tissue and serves as a source of oxygen-derived free radical [7].

A-Xanthine dehydrogenase/Xanthine oxidase is the major cytoplasmic source of superoxide radicals and hydrogen peroxide [8].

B-Xanthine oxido-reductase: a type of enzyme that generates ROS [9].

4) Alcohol dehydrogenase and Aldehyde dehydrogenase enzymes

Alcohol dehydrogenase and Aldehyde dehydrogenase enzymes are found in high levels in liver cancer cells and in serum due to the release of these enzymes from liver cancer cells [10]. Alcohol dehydrogenase enzyme converts ethanol (alcohol) to acetaldehyde. A highly reactive free radical known as 1-hydroxyethyl is created as a byproduct of this conversion [11]. The metabolism of acetaldehyde by aldehyde oxidase is source of free radicals which initiates lipid peroxidation [12].

5) Amino-oxidase enzymes

Amino-oxidase enzymes are present in high levels in tumor cells compared to normal cells [13]. There are two types of monoamine oxidase enzymes (MAO-A and MAO-B), which are found on the outer membrane of the mitochondria in most cell types of the human body [14].

The biochemical activity of monoamine oxidase generates Hydroxyl radicals [15]. The metabolism of polyamines by polyamine oxidase enzyme generates locally high concentrations of hydrogen peroxide [16].

High levels of phase l detoxification enzymes are shown in cancer cells. A sig-

nificant side effect of phase-I detoxification is the production of free radicals as the toxins are transformed, for each molecule of toxin metabolized by phase l enzymes, one free radical molecule is generated. So, phase-I detoxification enzymes are the major source of free radicals.

2.2.2. Phase-II Detoxification Enzymes

Phase I reactions are not sufficient to make the harmful substances water-soluble enough to complete the entire excretion pathway. The production of most phase II enzymes is controlled by a protein called nuclear factor erythroid-derived 2 (Nrf2). The presence of oxidative stress activates Nrf2, allowing it to travel to the cell nucleus [17]. In the cell nucleus, Nrf2 turns on the genes of many antioxidant proteins, including the phase II detoxification enzymes [18]. There are several families of phase II enzymes that differ significantly in their activities and biochemistry. A particular harmful substance can be detoxified by more than one phase-II enzyme.

1) Glutathione-S transferases (GSTs)

Glutathione-S transferases (GSTs) are major phase II detoxification enzymes present in several human tissues mainly in the cytosol. (GSRs) play a role in catalyzing the conjugation of electrophilic substrates to glutathione (a significant cellular antioxidant) [19].

2) UDP-glucuronlytransferases (UGTs)

They catalyze glucuronidation reactions; the attachment of glucuronic acid to harmful substances to render them less active and more water soluble. There are several different UGTs that are distributed throughout the body. In humans, many harmful substances are metabolised by UGTs [20].

3) Sulfotransferases (SULTs)

Sulfotransferases (SULTs) attach sulfates from a sulfur donor to harmful substances acceptor molecules [21].

GSTs, UGTs and SULTs catalyze the bulk of human detoxification reactions, several other phase II detoxification enzymes contribute to the process to a lesser, but still important extent, including:

A-Methytransferases enzymes catalyze methylation reactions using S-adenosyl-L methionine as a substrate [20].

B-Arylamine N-acetyltransferases (NATs) detoxify carcinogenic aromatic amines and heterocyclic amine [22].

C-Amino acid conjugating enzymes: Acyl-CoA synthetic and acyl-CoA amino acid N-acyltransferases attach amino acids (most commonly glycine or glutamine) to the harmful substances [23].

The conjugation reactions of phase II enzymes increase the polarity of xenobiotic substances by increasing water solubility.

2.2.3. Phase-III Detoxification-Transport

Phase-III transporters are necessary to excrete the newly formed phase II products out of the cell. Phase-III transporters belong to a family of proteins called

the ABC transporters (for ATP-binding Cassette [24]).

They require chemical energy, in the form of ATP, to actively pump harmful substances through the cell membrane and out of the cell [25].

The low level of phase-II detoxification enzymes result in an excessive amount of free radicals.

These harmful substances can be disposed of outside of the cells by activating phase-II and phase-III detoxification enzymes. The nuclear factor erythroid 2-related factor 2 (NrF-2) is sequestered in the cytoplasm by actin-bound cytosolic repressor Keap-1 [26]. Activated NrF-2 binds with response elements on DNA known as antioxidant response elements (AREs) and expresses several genes who stimulate the production of enzymes and who are involved in response to cellular stress, such as catalase and glutathione. These convert hydrogen peroxide (activator of NF-Kb) to oxygen and water [27] [28]. Also, NrF-2 is a potent inducer of phase-II detoxification enzymes [29]. So, NrF-2 has an effective role in clearing the cell of harmful substances. Thus, we can remove the harmful substances from cells by activating NrF-2.

There are certain dietary constituents including sulphoraphane from Broccli improves the expression of NfR-2, which stimulates the phase-II detoxification enzymes which, lead to increasing the polarity of harmful substances. Also, NfR-2 stimulates phase-III detoxification enzymes which pump them out cells.

2.3. Stage-3: Formation of Free Radicals

Free radicals are molecules, ions or atoms with unpaired electrons in their outer shell of electrons, which make them reactive due to the presence of unpaired electron(s).The reactive oxygen species (ROS) are oxygen-derived free radicals generated in the cell as byproducts of normal metabolism. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and non-enzymatic processes [30].

Accumulation of harmful substances in the cell results in activating the detoxification phase I enzymes. High activity of phase I detoxification enzymes results in excessive generation of free radicals as, (Superoxide anion and H_2O_2 which convert to hydroxyl radical, 1-Hydroxyethyl,aldehyde oxidase, Nitric oxide and peroxy nitrite).

Ionizing radiation, in the presence of O_2, converts hydroxyl radical, superoxide, and organic radicals to hydrogen peroxide [31].

Hydrogen peroxide (H_2O_2) is not a free radical as it does not contain any unpaired electron but can convert to hydroxyl radical [32].

The production of abnormally high levels of free radicals can be hazardous to the body and damages all major components of the cells, including cell membranes, carbohydrates, Proteins, and DNA [33] [34]. Excessive amounts of these free radicals can lead to cell injury and death which may contribute to many diseases, most importantly cancer [35].

The free radicals are controlled by the antioxidant system, both enzymatic and non-enzymatic.

Non-enzymatic antioxidants cannot be synthesized by the body and are obtained from food, such as vitamin C, A, and E.

Vitamin-C (ascorbic acid) inhibits protease enzyme allowing collagen fibrils to be restored and accumulate in extracellular space through 11 days [36]. Leading to the death receptor being in the proper position adheres to its ligand, thus, activating the extrinsic program of cell death.

Beta carotene inhibits the oxidant-induced NF-Kb activation and interleukin IL-6 and tumor necrotic factor alpha [37] [38].

Vitamin E is the major anti-oxidant vitamin in the body tissues and is considered the first line of defense against cell membrane damage. Vitamin E inhibits lipid peroxidation in cell membranes and prevents oxidative damage to DNA by scavenging free radicals.

Dietary vitamin E reduces the concentration of lipid peroxidase in live tissues through reducing their increased phospholipase A2 activity. Vitamin E reduces the accumulation of Superoxide radical and decreases the generation of oxidative damage substance [39].

Enzymatic anti-oxidants, such as, superoxide dismutase enzyme, can convert superoxide anions to hydrogen peroxide and dioxygen. Catalase and Glutathione enzymes which convert hydrogen peroxide (activator of NF-Kb) to water and oxygen [40].

Other compounds that have antioxidant activity include flavonoids [41] and N-acetyl-L-cysteine which increases the intracellular level of glutathione which works by donating the acetyl group to oxidized glutathione so that, it can be in a reduced form and works effectively.so, N-acetyl-L-cysteine serves as a co-substance to eliminate hydrogen peroxide (H_2O_2) and inhibit the activation of NF-Kb. [42] [43].

Tetrandrine is an alkaloid extracted from a Chinese medicinal herb. It is so potent, that 50 μg of it is sufficient enough to inhibit the activation of NF-Kb completely. Tetrandrine is an antioxidant for both superoxide and hydroxyl radical [44].

2.4. Stage-4: Activation of NF-Kb

At this stage the excessive H_2O_2 is produced directly by phase-I detoxification enzymes as (Cytochrome-P450, Xanthine dehydrogenase/oxidase, polyamine oxidase enzyme) and indirectly, by sodium dimustase enzyme which converts the superoxide free radical to hydrogen peroxide. Hydrogen peroxide (H_2O_2) plays a great role in the activation of NF-Kb. In unstimulated cells, both nuclear factor kappa B (NF-Kb) and dynein light chain (LC8) bind with inhibitor kappa B (IKB-α) in the cytosol of the cell forming (NF-Kb, -IKB-α, -LC8) complex.

LC8 inhibits the activation of NF-Kb by interacting with IKB-α. Thereby, preventing its phosphorylation by IKK. When cells are exposed to H_2O_2, the LC8 forms a reversible intermolecular disulfide bond between the two Cys^2 residues, leading to a conformational change that results in dissociation of LC8 from this complex while IKB-α and NF-Kb remain bound together [45]. This dissociation

of LC8 from (NF-Kb, IKB-*α* and LC8) complex allows the IkB kinase enzyme (IKKs) to phosphorylate the inhibitor kappa B (IKB-*α*). This phosphorylation results in dissociation of IKB-*α* from NF-Kb. Finally, NF-Kb becomes free and trans locates into the nucleus and stimulates the expression of several genes including the genes that play a direct role in the shutdown of the intrinsic and extrinsic programs of cell death as (Muc-1, Bcl-2, MMPs and Decoy-R3) and the genes that play an indirect role as TNF-*α* gene which stimulates the expression of (Muc-1, Muc-4 and Muc-16). Also, it is responsible for the production of cytokines.

The cytokines, which are stimulated by NF-Kb, activate the IKB kinase (IKKs) which phosphorylates IKB-*α* leading to the reactivation of NF-Kb, thus, establishing a positive auto regulation loop that can amplify the inflammatory response and increase the duration of chronic inflammation (**Figure 1**) [46]. Therefore, a normal cell passes through several stages (accumulation of harmful substances, high level of phase-1 detoxification enzymes, excessive H_2O_2 and super oxide free radicals, activation of NF-Kb and shutdown the intrinsic and extrinsic program of cell death) to convert into a cancerous cell.

Glutathione is the most important antioxidant for neutralization of free radicals by donating it electron to H_2O_2 reduce it into $H_2O + O_2$ [41].

The ratio of the main active form of glutathione (the reduced glutathione)

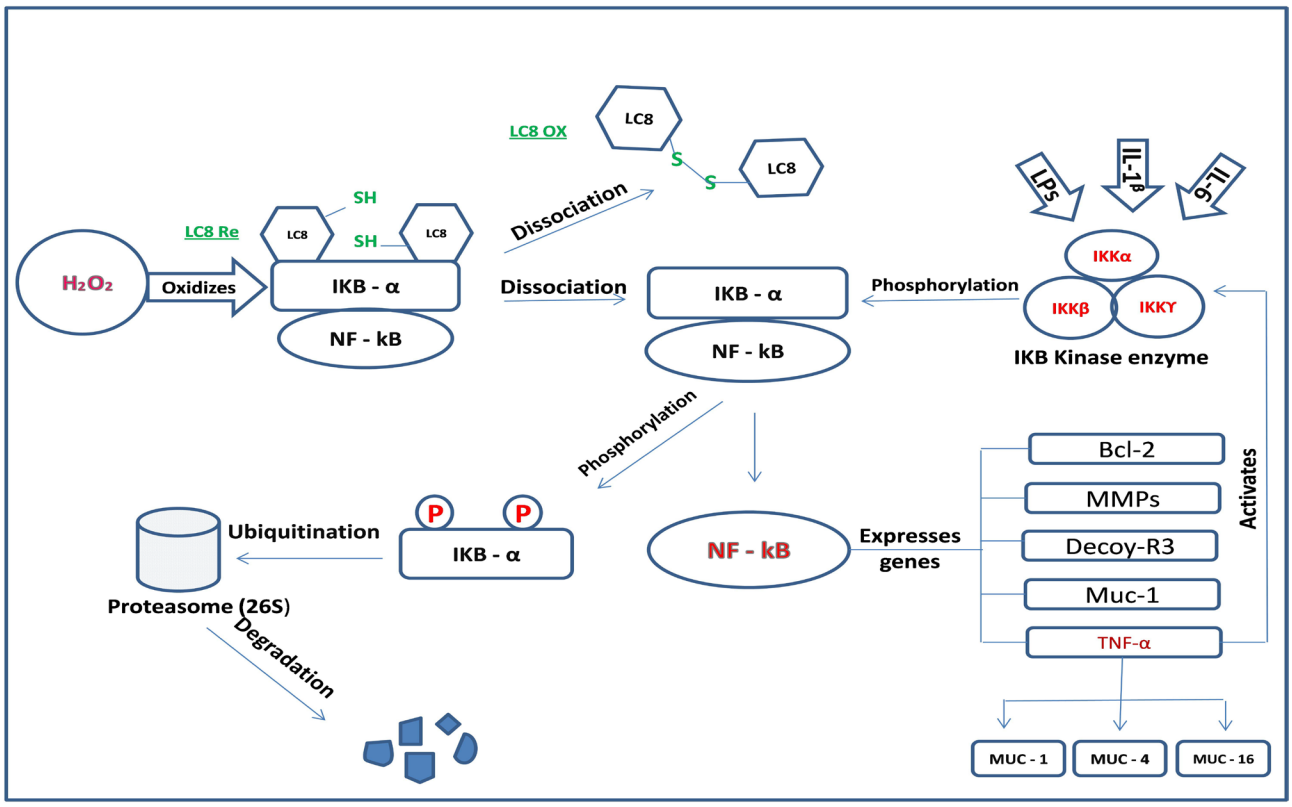

Figure 1. Shows H_2O_2 oxidizes the LC8 leading in dissociate it from IKB-*α*, [45] then IKKs phosphorylate the IKB-*α* resulting in free NF-Kb, which Trans locates into nucleus and stimulates the expression of genes which responsible for shutdown the pathway of the intrinsic and extrinsic programs of cell death. TNF-*α* reactive the NF-Kb by stimulates LKKS [46].

to in active form (the oxidized glutathione) within cells is often used as a measure of cellular toxicity and carcinogens. The reduced glutathione for GST conjugation depends on adequate dietary in taking of sulfur-containing amino acids (methionine or cysteine), vitamin B6 for the conversion of methionine to cysteine, as well vitamins B2 and B3 for the activity of glutathione reductase, which recycles oxidized glutathione.

Cysteine is the critical amino acid needed for synthesis of glutathione (GSH). VitaminB2, B3 and B6 and Cysteine are needed for production and maintenance of the active form of glutathione [42].

Selenium is an essential trace element and co-factor glutathione peroxidase.

Cur cumin improves the active form of glutathione (reduced glutathione) [41].

N-acetyl-L-cysteine increases the intracellular level of glutathione which works by donating the acetyl group to oxidized glutathione so that it can be in a reduced form and work effectively. So, N-acetyl-L-cysteine serves as a co-substance to elimination H_2O_2 and inhibits the activation of NF-Kb [42] [43].

3. Results and Discussion

The accumulation of harmful substances in the cells results in elevation of the level of the phase-I detoxification enzymes as (Cytochrome P450, Xanthine-oxidase and Amino mono oxidase). High levels of phase-I detoxification enzymes or exposure of the cells to ionizing radiation results in generation of hydrogen peroxide (H_2O_2) and free radicals especially super oxide free radical.

The excessive amount of H_2O_2 is produced either directly as a byproduct of phase-I detoxification enzymes processing or indirectly by sodium dismutase enzyme which converts the super oxide free radical to H_2O_2.

Hydrogen peroxide oxidizes the dynein light chain (LC8) which binds with inhibitor kappa B (IKB-α) and forms a reversible intermolecular disulfide bond between the two Cys^2 residues leading to conformational changes that results in dissociation of LC8 from IKB-α. But IKB-α remains bound to NF-Kb in the cytosol. This means that the NF-Kb is still in an inactive form.

The IKB kinase (IKKs) phosphorylates the inhibitor kappa B (IKB-α).This phosphorylation results in dissociation of IKB-α from NF-Kb. The NF-Kb becomes free and translocates into the nucleus and stimulates the expression of several genes that are responsible for blocking the pathways of the intrinsic and extrinsic programs of cell death. So, H_2O_2 is the first step for activation of NF-Kb followed by phosphorylation by IKKs. The activated NF-Kb is responsible for the cell fleeing from death and its conversion to cancer cell [47]. However, the normal cell passes through several sequential stages to flee from death and convert into a cancerous cell.

We planned a therapeutic strategy of cancer; this strategy depends on making the programs of cell death run again.

The planned therapeutic strategy can work if one stage is blocked completely, as this stage is necessary for cancerous conversion. However, completely shut-

ting down all stages is the most comprehensive therapeutic strategy and guarantees treatment success. It can be performed through these steps:

1) Removing the harmful substances from cells by increasing phase-II and phase-III detoxification enzymes.

2) Regulating the phase-I detoxification enzymes (normal level).

3) Scavenging of free radicals.

4) Decomposition of H_2O_2.

5) Inhibiting NF-Kb activation and preventing it is binding to DNA. NF-Kb can be kept in an inactive form by controlling of H_2O_2 and IKKs.

This strategy can be applied via a therapeutic program or diet program.

First, the therapeutic program

1) Sulforaphane

This compound improves the expression of the nuclear factor Nrf2, which stimulates the production of the phase-II detoxification enzymes which contributes to the removal of harmful substances from cells [48].

2) Polyphenol

This compound stimulates phase-III detoxification enzymes which pump the harmful substances out of the cells.

3) Estimating the levels of phase-I detoxification enzymes specifically cytochrome P450, Xanthine oxidase and amino oxidase enzymes and reduce them to the normal level to avoid the production of more free radicals. There are more inhibitors. For example xanthohumol is inhibitor of cytochrome P450. Allopurinol is an inhibitor of Xanthine enzyme at dose100-300 mg and curcumin is an inhibitor of both MAO-A and MAO-B. The phase-I detoxification enzymes are responsible for generating superoxide free radical and H_2O_2 is shown in **Table 1**.

4) Antioxidants supplementation

Non-enzymatic antioxidants, these the body cannot synthesize and are obtained from food, such as vitamin A, E and C. The doses recommended in this paper are higher than the daily requirements to ensure complete neutralization of the free radicals. Vitamin C at high dose (2000mg/day) is without risk. Also, vitamin E at high dose (3200mg/day) is without risk. But large intakes of Beta Carotene must be supervised or used with caution, as they have been shown to make lung cancer worse [33].

Vitamin C inhibits protease enzyme allowing collagen fibrils to be restored and to accumulate in the extra cellular space, in 11 days. The recommended dose

Table 1. Show the major phase-I detoxification enzymes and their inhibitors and recommended dose.

Enzyme	Inhibitor	Recommended dose
Cytochrom P450	Xanthohumol	50 MUG
Xanthine-oxidase	Allopurinol	100 - 300 MG
Amino-mono-oxidase	Curcumin	10 G

is 400 mg three times daily [36].

Vitamin E reduces the accumulation of superoxide radical, so H_2O_2 formation is reduced. The recommended dose is 400 mg three times daily [49] [50].

Beta-Carotene inhibits oxidant induced NF-Kb activation. The recommended dose is 400 mg twice daily [37] [38].

B-Enzymatic antioxidants such as (Glutathione and Catalase), these decompose hydrogen peroxide to water and oxygen to avoid its oxidation of CL8, as well as preventing the dissociation of LC8 from the IKB-α, which prevents IKKs action, thus preventing the activation of NF-Kb. The recommend dose of glutathione is 50 mg twice daily with selenium and N-acetyl-L-Cysteine, this structure maintains the activation of glutathione. It is available in the market as a combination.

The inhibitory effects of Aspirin and sodium salicylate result from the specific inhibition of ATP-binding to IKKβ. Thus, IKKβ-dependent phosphorylation of IkB-α is reduced preventing the activity of NF-Kb pathway [51].

Also, inhibition of proteasome function prevents IkB-α degradation. A group of boronic acid peptides, including PS-341, are extremely potent inhibitors of proteasome function. Also, inhibitors of ubiquitin ligase mediate IkB ubiquitin [46].

Another suggested therapeutic program

It is composed of this combination (Tetrandrine 5 μg, glutathione 50 mg and aspirin 25 mg + VIT C, A and E). Tetrandrine 5 μg completely blocks superoxide free radical. If Tetrandrine 5 μg does not completely shut down free radicals production, glutathione 50 mg can act as a backup by decomposing H_2O_2 and preventing oxidation of CL8. Aspirin table 25 mg prevents the activation of IKKs, thereby preventing phosphorylation of IKB-α and keeping NF-Kb inactive.

Second, dietary programs

1) Grapefruit contains naringenin (the principle flavonoid in grape fruit), hesperetin and eriodictyol which reduce the cytochrome P450, which represents the bulk of oxidation processing. The recommended amount is 200 ml juice [52].

2) Red grape and cherries, containing high level of flavonoid (anthocyanidins and cyanidin) which inhibits Xanthine enzyme and amino mono-oxidase enzymes. A quantity of no less than 1/2 kg/day is recommended. Also black grapes and blackberries are high in the flavonoids epicatechin and catechin [53].

3) Broccoli contains sulforaphane, which activates the nuclear factor (Nrf2) and stimulates the production of phase-II detoxification enzymes. The recommended quantity is 1/2 kg/daily [48].

4) Apples, contain polyphenol, which increases the production of phase-III detoxification enzymes which pumps the polar harmful substances out of the cells [54].

5) Turmeric contains the curcumin which is a potent activator of E-cadherin expression and prevents the activity of the nuclear factor Kappa B and inhibits

both MAO-A and MAO-B and increases the level of Serotonin and Dopamine [55]. The recommended dose of curcumin is 10 grams in a glass of milk per day.

6) Glutathione is a dietary supplement which decomposes H_2O_2 to $H_2O + O_2$. The recommended dose is 50 mg twice daily [40].

7) The recommended dose of vitamin A, C, E is 400 mg three times a day.

8) Aspirin 25 mg three time daily.

9) Program of food for 8 days to 11 days, during which the cell restores collagen which is necessary for cell adhesion and up righting the death receptor position to facilitate adhesion of its specific ligand which allows the extrinsic program of cell death to run again.

In the case of lymphoma, the program may need to be applied for a long time

The cure percentage will be 100% if only one program of cell death (the intrinsic or extrinsic) runs again and will be 200% if both programs (the intrinsic and extrinsic) run again. But 50% of human cancers have mutations in the p53 gene which lead to loss the activity of the gene [56]. It means that the patients lost the intrinsic program of cell death and the cure must depends on the running their extrinsic program only. Thus, the patients who have gene P53 the cure percent among them will be 200% and the patients whom have lost the activity of gene P53 the cure percent among them will be 100%. So, the cure percent of this therapeutic strategy among all patients is 150%.

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