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REVIEW ARTICLE

A Rethinking on the Benefits and Drawbacks of Common Antioxidants and a Proposal to Look for the Antioxidants in Allium Products as Ideal Agents: A Review

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Abstract This review article on the beneficial uses of Allium antioxidants tries to give some answers to the recent doubts raised by Singh et al. (Ind J Clin Biochem 25(3):225–243, 2010) against the claim of some researchers that Antioxidants (AOs) are miraculous molecules. Many people still believe that vitamins like A, C and E are the only true AOs that play important role in the corrections of metabolic derangements in life style diseases and hence all their faults are attributed to the failures of AOs as a class. This is quite unfair as there are many other natural AOs that do equal or even better AO action than the vitamins. Such is the case with the Allium S-alkyl sulfoxide aminoacids and their breakdown products viz, the various poly sulfides and their oxides e.g. allicin and ajoene type compounds which trap electrons mainly. It is true that antioxidant vitamins and β-carotene a precursor of Vitamin A bring about problems as prooxidant or as agents that block some metabolic pathways and gene expression. Again the argument that AOs cannot improve the level of antioxidant enzymes like SOD, catalase and glutathione Px is also not universal. Actually allium AOs can even spare the use of antioxidant vitamins in the body and enhance the action of antioxidant enzymes and supply of ATP and other nutrients to the tissues as the former are good vasodialators and promoters of membrane permeability. The use of AOs should be selective and moderate. Allium AOs satisfy the role of ideal AOs based on many of their invivo and invitro actions reported by the author and others. Their metabolits can regenerate them and recycle them for a sufficient time in the body. They have non antioxidant effects also such as antiplatelet, fibrinolytic, anti-inflammatory, immunomodulatory, antiageing actions etc. Plant derived AOs may be more beneficial and better tolerated in their partially purified forms rather than in their absolutely purified forms as the accompanying principles have some protective and regulatory effects in general. This and other aspects of allium AOs are discussed in the paper.

Keywords Ideal antioxidants · Allium disulfides and their oxides · Vitamins C & E · β-Carotene · Non antioxidant effects · ROS

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Introduction

In two recent articles by Singh et al. [1, 2] they raised some thought provoking arguments against the time old claims that antioxidants (AOs) are miraculous molecules that can prevent or cure many serious diseases such as cancer, heart problems, aging etc. At the very appearance of the title of Singh's second article [2], the senior author of this paper (KTA) was taken aback and thought that all his seventy and old papers (during 1960–2010) were simply a waste. But on perusal of the two articles we are convinced of the points that the use of AOs should be selective and moderate

only and not a total negation of all the findings on AOs is recommended. The major points raised by Singh et al. [2] may be summarized and accepted as follows.

1. Several AOs are essential for life but excess of them may lead to suppression of all ROS and RNS which have also decisive roles in low concentrations in metabolic reactions and for modulation of many pharmacological processes.
2. AOs are cell specific and radical specific but they are not universal effectors of all genes.
3. Actions of various AOs may differ in vivo and in vitro and they can perform several non-antioxidant activities highly beneficial to the cell.

However we may add another relevant point here as an addition to the above that.

4. Antioxidant vitamins A, C & E and β-carotene are not ideal antioxidants for all purposes and hence our conclusion should not be based on their performances only.

The aim of this article is to join with the arguments of the previous authors where ever it is possible as well as to give some explanations as to why some strong antioxidants like vitamins C&E, epigallocatechin gallate (EGCG) or β-carotene fail in carrying out their expected roles as miraculous molecules in preventing or curing certain diseases. Pills or any other purified forms of AO may be a failure as they are devoid of several other protective ingredients present along with the AOs in the plants or their extracts. The purified AOs become over active as reported by Singh et al. [1]. This may be due to lop sided disturbances in AO network or deregulating other metabolic activities. This hindrance in the actions of AOs brought about several drubbing outcome including increased morbidity and mortality.

The so called vitamins C in citrus fruits, E in germinated seeds and vegetable oils, and β-carotene in carrots, lycopene in tomatoes, EGCG in green tea [3], sulfoxides and polysulfoxides in alliums or their extracts [4–7] may be in minute quantities only in each serve of the items in a menu. Such minute quantities of AOs mostly present in much acclaimed Mediterranean, Chinese and Indian foods may give a guideline for arriving at a moderate concentration of AOs for a healthy practice of foods. In these countries e.g.; in Mediterranean areas olive oil, grapes/wine and in China various mushrooms like ganoderma lucidum and plant foods made of onion/garlic and in India sun flower, safflower, sesame and mustard oils, onion, garlic, cabbage and broccoli present in food along with spices like turmeric, ginger, cumin, cardamom, cloves etc. are used in plenty. All the above food materials contain a cock tail of AOs as described in the book on nutraceuticals and else where [4–9]. Daily use of any such plant product as a food supplement singly or in combination may help the body to scavenge the day to day production of ROS and RNS due to alcoholism, smoking, over eating or any injury/disease in the body. The plant products described above contain several health nutrients like bulk and trace elements essential to our body in addition to AOs, mono and poly unsaturated oils. If we moderately use them every week by turn we get a cock tail of AOs and other nutrients in sufficient but not in excess forms. But out of fear of ROS & RNS if we over load our body with the above items, we shall be destroying all oxidants and producing harmful metabolites of AOs as argued by Singh et al. [1, 2] This situation also curtails the chances of ROS and RNS to play their role in destroying microbes and also in inducing certain genes [8] responsible for the production of AO enzymes. However the use of plant extracts or their raw forms may do less harm than the pure forms of pills of each e.g.; vitamins C&E and β-carotene [10–15]. The beneficial nutritional medicines present in plant products like resveratrol in wine, flavonoids and polyphenols in fruits and poly sulfides in alliums are called nutraceuticals as described in our book [4] in 2009. Nutraceuticals are classified into five main groups, viz; (1) Terpenes including the subclasses of caroteniods and limonoids, (2) Phytosterols, (3) Polyphenols (4) Flavonoids/isoflavonoids and (5) Theols containing various organosulfides and polysulfoxides. It is note worthy to say that they are mostly AOs e.g.; β-terpinene and β-carotene are terpenes and its polymer, withaferin A, isolated from Ashwaganda is a steroidal lactone, epigallocatechin is a polyphenol, quercetin is a flavonoid, ajoene is a polysulfoxide and a polymer of allicin (a theol isolated from garlic extract). They are all well versed AOs with very many therapeutic actions [4, 10, 16].

Some Unread Parts of Antioxidants with Respect to their Structures and Toxicity

The antioxidant actions of nutraceuticals are due to functional groups like phenolic or enolic hydroxyls, conjugated dienes, sulfoxides and the like that can donate an electron (with or without a hydrogen atom) to a reactive oxygen species. As ascorbic acid (Vitamin C) has two enolic hydroxyl groups it can scavenge two ROS moieties, while vitamin E with only one phenol group can scavenge only one ROS. Caffeic acid has two phenolic groups, gallic acid has three such groups, epicatechin (EC) and quercetin have four such groups, epigallocatechin (ECG) has five and epigallocatechin gallate (EGCG) has eight hydroxyl groups respectively. Therefore they can scavenge 2, 3, 4, 5, and 8 ROS groups respectively. As the first two AOs are moderate antioxidants the other 4 phenolics viz; quercetin, EC, ECG and EGCG are very strong antioxidants.

This may be the reason that when the last two poly phenols as very strong antioxidants can damage human lymphocyte DNA, caffeic acid and quercetin only with 2 and 4 phenolic groups could give DNA a protective effect through their antioxidant action in ex vivo experiments [2]. However vitamin C & E or EC could not give any protective effect to DNA. The reason may be that their antioxidant actions might have been nullified by the action of their metabolites on reduced thiols like GSH which are endogenous AOs for vitamin regeneration, and accompanied inhibition of gene induction due to sweeping away of ROS and RNS [1, 17]. This type of GSH exhaustion can be avoided with such AOs which trap electrons, regenerate themselves and enhance GSH production. Alkyl and alkenyl disulfides and their sulfoxides are capable of doing these feats with very little quantities of each according to Klans-Dieter [18] and our findings [19, 20].

The mechanism of action of organic disulfides/sulfoxides in which R=CH_3, C_3H_5, C_3H_7, etc. is

$$2RS\,S(O)\,R_1 + e^- aq \rightarrow RSSR_1^{-\bullet} + RSS(O_2)R_1$$

(disulfide oxide) (disulfide radical ion and thiosulfonate)

$$RSS - R_1^{-\bullet} \rightarrow RS^{\bullet} + R_1S^-$$

(Disulfide redical ion) (Free radical & Sulfide anion)

$$RS^- + OH^{\bullet} \rightarrow RS^{\bullet} + OH^-$$

(Free radical repair)

$$RS^{\bullet} + RS^{\bullet} \rightarrow RSSR \text{ (Termination)}$$

Disulfide and thiols can also scavenge free radicals

$$RSSR + OH^{\bullet} \rightarrow RSOH + RS^{\bullet}$$
$$RSH + OH^{\bullet} \rightarrow RS^{\bullet} + H_2O$$

The thyl radical $RS^{\bullet}$ helps in the repair of free radicals and it does not react with critical molecules, hence they serve as very good scavengers of free radicals and as antioxidants. These disulfides, their polysulfides and sulfoxides are formed in the crushed or ground pulps of onions, garlic and cabbages and in the extracts of asafoetida. A small amount of these disulfides can scavenge any number of free radicals by a cycle of actions by repair, regeneration and electron trapping as shown in the equation. These types of free radical repair reactions prevent tissue damages and lipid peroxidations particularly in liver and heart [4]. Garlic & onion aminoacid sulfoxides viz; S-allyl cysteine sulfoxide, S-propenyl cysteine and S-methyl cysteine sulfoxides produce by the action of alliinase their degradation products called garlic and onion oils which contain diallyl, dimethyl, allyl methyl, allyl propyl or propenyl sulfoxides and corresponding disulfides and polysulfides.

In the allium oils, on storage besides the disulfides their more active disulfide oxides viz; allicin (C_3H_5–S–S(O)–C_3H_5), its polymer ajoene (C_3H_5–S(O)–C_3H_4 S–S–C_3H_5) and related allicin type and dithiin compounds are formed in varying quantities. Hence these oils and their precursor amino acids (see their equation given below by Cavallito & Bailey) have many medicinal effects including antibiotic, antioxidant, hypotensive, antiinflammatory, antiplatelet aggregation, fibrinolytic and many other effects [21–23].

Onion and Garlic are Good Sources of Ideal and Multifunctional Antioxidants

It is worthwhile to consider garlic and onion oils as ideal antioxidants in very low doses based on their medicinal effects reported from many centers of research [4, 21]. This is all the more important when we consider their moderate antioxidant activity, least toxicity as well as their capacity to get detoxified as CO_2, SO_2 and water. Moreover they are ingredients of the day to day diet of many nations from prehistoric time (e.g.; Norway, Germany, Egypt, China & India) Therefore specific quantities of onion & garlic or their standardized products e.g.; Oils, aged garlic extract (AGE), garlic powder extract, onion extract etc. can be added to our menu according to the choices of each one. Alternatively garlic creams or slices of onions can be added as ingredients to salads.

Antioxidant Actions of Allium Products

The precursors of allium oils viz; the sulfoxide amino-acids in onions & garlic are palatable, mild & less smelling antioxidants available through extracts of sliced garlic & onions (Here the action of alliinase enzyme is minimized and hence oil is not formed). If the alliums are crushed the enzyme alliinase acts on the sulfoxide aminoacids e.g.; SMCS, SACS, SAPS etc. and yield oils, i.e. the sulfoxides of their alkyl and alkenyl di sulfides viz; diallyl disulfide oxide (DADSO) or allicin and allyl methyl disulfide oxide (AMDSO) from garlic and ally propyl disulfide oxide [APDSO], AMDSO and allyl propenyl disulfide oxide(AP(en)DSO) from onions. The major product of garlic is allicin and that of onion is 'type compound AP(en)DSO. The action of alliinase which is released from the vacuoles of alliums e.g.; garlic was illustrated by Cavallitto and Bailey [23]. A = Allyl; M = Methyl; P = Propyl; P(en) = propenyl groups. These groups are represented by R in sulfoxide amino acids, and R1 to Rn for mixed disulfides, their sulfoxides and thiols.

$$2R-S(O)CH_2.CH(NH_2)\ COOH\ +H_2O \xrightarrow{Allinase} R-S-S(O)R\ +\ 2CH_3COOH\ +\ 2NH_3 \quad (1)$$

(Allicin) (Pyruvic acid)

The allicin type compounds can oxidize cysteine and various protein thiols and form allyl derivatives according to the studies of the above researchers

$$R_1-S-S(O)-R_2+2R_3SH \rightarrow R_1-S-S-R_3 + R_2-S-S-R_3+ H_2O \quad (2)$$

Allicin / Allicin type comp. (Disulfide)

$$R_1-S-S-R_3+R_2\_S-S-R_3 \rightarrow R_1-S-S-R_2+R_3S-S-R_3 \text{ or } R_1-S-R_3 + R_2-(S)_3-R_3 \quad (3)$$

$$R_1-S-S-R_2+R_3\_SH \rightarrow R_1-S-S-R_3+R_2SH \quad (4)$$

Allicin works as prooxidant and carry out disulfide exchange reactions. When thiols are oxidized they become part of new disulfides and monosulfides or form allyl thiol or mercaptan as in reactions 2–4. As allicin is immediately converted to ajoene and poly sulfides the pro oxidant action is possible only with freshly crushed and extracted garlic and onion. Their oils are devoid of allicin and harmless to bacteria but biologically active in other ways e.g.; antiinflammatory, immunomodulatory, antiplatelet aggregation etc. in action.

Allicin and derived disulphides can trap electrons and undergo the chain breaking reactions that involve free radical scavenging as shown before by Klans-Dieter [18] (see equations in back pages). Mei et al. [24] reported from China that the antioxidants and vitamin C in garlic, a dietary constituent for many people of China possibly block the conversion of nitrates in food to nitrites and they might act as anti- promoters of cancer. If nitrites are formed in the stomach they convert amines to nitrosamines which are carcinogens. Mei [24] noted the absence of nitrites in the gastric juice of people who ate regularly garlic as part of their food. In a series of studies Lau and associates [26–28] demonstrated that several garlic compounds can minimize oxidation of LDL cholesterol in vitro. Short term supplementation of garlic in human subjects has demonstrated an increased resistance of LDL to oxidation [29]. As the sulphoxides and di and polysulphides are similar in nature and action for both garlic and onions, special attention should be focused on the antioxidant role of onion principles also. The antioxidant effect of onion oil was compared with that of garlic oil and vitamin E in nicotine administrated rats by the senior authors' team [19, 20]. Nicotine administration (0.6 mg/kg/day) for 21 days to a group of rats increased lipid peroxidation in their tissues viz; liver, lungs, heart and kidney. On simultaneous feeding of each of onion and garlic oils and vitamin E separately to different nicotine injected groups at a dose of 100 mg/kg/day for 21 days each of them ameliorated the alterations in lipid peroxidation. The increased peroxidation products like TBARS, hydroperoxides and conjugated dienes decreased significantly in all treated groups as compared to nicotine injected control groups.

Further the decreased enzyme activities of catalase, superoxide dismutase and glutathione peroxidase in the tissues were raised significantly to near normal levels in all the treated groups. GSH level was also improved simultaneously. Again the use of allium oils/SACS increased the level of vitamin C and E and retinol in liver tissues significantly as compared to the nicotine control group. These results support the A.O action of allium oils comparable to vitamin E. The order of their activities was vitamin E = garlic oil > onion oil.

The higher activities of vitamin E and garlic oil may be due to the presence of unsaturated double bonds in phenol ring and in place 2 at the outer end of allyl group respectively for them. In onion oil disulphide only methyl, propenyl and propyl groups are present. The unsaturated bond in propenyl group is in position 1 i.e., close to the sulphur bond and this make it a weaker antioxidant. Alkyl groups like CH_3 & C_3H_7 are still less helpful for antioxidant action. Saturated groups weaken the antioxidant actions of onion oil. Moderate hypoglycemic, hypolipidemic and antioxidant effects were observed with the onion oil and their precursors like SMCS and SP (en) CS and garlic oil and its precursor SACS, in diabetic rats and alcohol fed rats [30–36]. As observed above on consuming extracts of garlic or onion or their oils and their precursor aminoacids significantly improved the condition of diabetic rats and humans according to the measurement of their blood sugar, blood lipids, GTT, lipid peroxidation, enzymes etc. The deleterious effects of alcohol feeding in rats viz; increase in lipid factors, lipid peroxidation, decrease in antioxidant enzymes viz; catalase and SOD and increase in HMG Co A reductase, the rate limiting enzyme in cholesterol synthesis were ameliorated and brought towards near normal level by feeding SACS isolated from garlic. These effects make allium principles as very important nutraceuticals that can correct the derangements in the metabolic system of diabetes. The antioxidant action of allicin is attributed partly to inhibition of NO production by cytokine induced NO synthase [37].

Other Important Effects of Allium Principles

Hepato Protective Action

Prophylactic effects of garlic oil, its non polar fraction and an anthocyanin isolated from banyan tree bark were

observed as compared to vitamin E in CCl_4 administered rats.

A very encouraging result in the form of correcting the hepatic damages by CCl_4 in rats was observed on simultaneous feeding of the above nutraceuticals [38].

When CCl_4 at a dose of 3.2 g/kg/72 h (every 3 days) was administered to rats for a month i.e., ten feedings, it increased significantly the serum and tissue lipid profile and deranged the enzyme activities of ALP, ALT, AST, glutathione reductase, HMG Co A reductase, catalase, glucose 6-PDH, and malic enzyme in rats. Simultaneous administration of garlic oil (G.O), its non polar fraction (NPGO), lecuopelargonin (anthocyanin) isolated from the bark of banyan tree (F.bengalensis Linn.) and vitamin E, at a dose of 100 mg/kg/day orally for the first three items and 50 mg/kg/day for the vitamin, intraperitoneally for a month to different groups of CCl_4 fed rats, the hepatic damages as well as the alterations in parameters such as serum, liver and heart lipids, lipid peroxidation, serum proteins, A/G ratio and the above sited enzymes were significantly corrected towards normal values. The degree of the effects was almost same for each sample used. In the correction of liver damages the order of effects of each sample was garlic oil > NPFGO > anthocyanin > vitamin E. This was evident from the histopathological examination of the diagram of liver slices. The modulatory effect of garlic oil has been attributed to polysulphides as they increase glutathione-S-transferase activity and lower N-nitroso di methylamine demethylase activity [39].

Cardio Vascular Protective Effects

A detailed mortality study [40] on patients who had prior heart attacks showed that in those given gelatin capsules containing garlic oil (6 mg/kg/day) high in ajoene and dithiins for 3 years, there was a significant reduction in serum lipids, a 35% reduction in new heart attacks and a 45% reduction in total deaths compared to control group. Allicin is an inhibitor of acetyl Co A synthesis [41], and diallyl disulphide (DADS) is an inhibitor of HMG Co A reductase, the rate limiting enzymes of cholesterol synthesis [42]. These findings support the use of onion and garlic or their products for preventing CVD in humans.

Antiinflammatory Effects

Thiosulfinates viz; allicins and cepaenes (onion principles) have been shown to possess antiinflammatory properties [43]. This action in part is related to inhibition of inflammatory cell influx by thiosulfinates and cepaenes. Ajoene shows anti-inflammatory activity similar to that of the drug indomethacin [44]. Inflammation is related to the action of cyclooxygenase that promotes prostaglandin synthesis. Allicin and related sulfides inhibit cyclooxygenase action [45, 46].

Platelet Aggregation Inhibitory Activity

According to Lawson et al. [45] an interaction product of allicin with endogenous thiol viz; S-(allyl thio) cysteine may be responsible for much biological effects of garlic within the body. Several studies indicated that components of freshly cut garlic or onions that contain allicin type compounds inhibit platelet aggregations and smooth muscle contraction through inhibition of cyclooxygenase and related enzymes [46]. Ajoene shows a significant activity in preventing loss of platelets and in increasing the rate of restoration of platelet clotting activity. Ajoene can also inhibit adhesive interaction of human neutrophils and consequently effect in vivo super oxide anion formation. This is an illustration of antioxidant property of garlic and onion principles [21, 41]. Mahkeja et al. [47, 48] have demonstrated that garlic and onion oil fractions containing allicin or poly sulfides effectively inhibited ADP, arachidonic acid or collagen induced platelet aggregation. This property of allium oils is due to their blockage of thromboxane and prostaglandin biosynthesis through inhibition of fatty acid oxygenases. Methyl allyl trisulfide was shown to have a more potent activity than other sulfides. Allicin and related sulfur linked compounds (thiosulfinates) are implicated in a principal source of the antiplatelet property of garlic juice and are significantly more potent platelet inhibitor than aspirin at nearly equivalent concentration [49]. They inhibit platelet aggregation and micro particle shedding at a calpain—dependent [50] step. The antiatherogenic action of garlic may be related to its inhibitory influence on geranyl–geranyl transferase I(GGT- ase I) [50]. Di allyl trisulphide a break down product of allicin shows antiplatelet activity and inhibits formation of thromboxane [51]. Allyl methyl trisulphide inhibits the arachidonic acid cascade at the reaction site with PGH synthase and specifically inhibits the conversion of PGG_2 to PGH_2 [52].

Aggregation inhibition by fresh juice of onion varied with time showing induction of aggregation in the initial time period following juice preparation which was dissipated after 30 min, as well as platelet inhibition which increased as the onion extract aged [53]. In fresh garlic and onion juices allicin type compounds are initially formed. It takes time for them to get transformed into alkyl or alkenyl poly sulfides which are the true inhibitors of platelet aggregation e.g.; DATS, DMTS, AMTS etc.

Effect on Blood Pressure

Blood pressure reduction has been observed by Damurau [54] upon administration of garlic extract in 85% of his

patients. In one study in China [55], on 70 hypertensive patients who were given garlic oil equivalent to 50 g raw garlic/day, 47 patients showed moderate to marked reduction (62% success) in BP. In yet another study in Germany [56], on administration of garlic powder to 24 hypertensive patients for 3 months, their supine diastolic blood pressure fell by 11% and their standing systolic pressure fell by 12% as compared to non significant fall in a control of 23 patients. Similar results were obtained by Petkov in Russia also [57]. Onion and garlic organic sulfides can combine with NO and enhance vasodialation and reduce hypertension in mammals according to Ku et al. [58] and Schwartz et al. [37]. A similar effect is proposed for the anti hypertensive effect of onion in spontaneously hypertensive rats [59]. WHO recommends to use crushed fresh garlic (2–3 cloves/day) to prevent hypertension.

Antibiotic Activity

Allicin and related compounds (thiosulfinates) are formed on crushing garlic [23]. Allicin type and related compounds are formed in crushed onions [28, 60]. Anti microbial effect of allicin on both gram negative and gram positive bacteria is considerable even at a 1:100,000 dilution. Albert Schweitzer [61] first treated amoebic dysentery in Africa with garlic only. Antimicrobial effects of allicin type compounds from onions are weaker as the double bond in the alkeyl group is at position 1 rather that at 2 as in allicin. Onion juice is a home remedy to cure eye infections (e.g.; conjunctivitis) in Kerala and this is because it does not harm eye as strongly as garlic juice. In bruised parts of fingers a bandage with bruised onion is also useful to cure the injuries. Alternately for the same purpose bruised garlic can also be used in bandages. If 2–3 garlic cloves are consumed/day for two to 3 days, the injuries on the body get cured easily without pus formation. The senior author used these methods several times to cure injuries under the nails of the feet and also tooth ache. If we chew 1–2 cloves of garlic daily for a few days any severe tooth ache can be cured quickly. When we get tired and not able to get tea or coffee, eat 2–3 cloves of garlic by chewing them and swallowing them with a glass of water. This can be explained by the findings of Bogin [62]. According to him allicin type compounds drive the ATP molecules from the blood stream into RBC and mitochondria and possibly increase the permeability of ATP through all biological membranes and supply energy to muscles. This study needs further investigations. Diallyl trisulfide a constituent of garlic oil has been used in China to treat viral infections and cryptococcal meningitis [63]. Ajoene also possesses significant antifungal activity inhibiting the growth of a number of fungi [64]. Few days garlic pulp consumption prevents infections from jaundice and chinkunguniya [7].

Immuno Modulatory Effects of Garlic Principles are related to Their Anti Carcinogenic Action

Garlic principles stimulate the body's immune system, particularly enhancing the macrophages and lymphocytes, which destroys bacteria, virus and cancer cells.

Dr. Benjamin Lau an eminent immunologist and former professor of Loma Linda University wrote in his book [65] that garlic can help to inhibit tumour growth and his experimental data show that garlic can do this through enhancing the body's own immune system. When garlic extract (Japanese kyolic) was injected subcutaneously and intraperitoneally the latter method produced more leucocytes activity assessed by a method of chemiluminescence in mice. Lau believes that garlic principles through immunomodulation can inhibit the growth of virus cells and nullify some of the toxins that impair the immune system. These are very good attributes for a neutraceutical. The four groups of immune cells are B lymphocytes, T lymphocytes, the phagocytes and the natural killer cells [66]. In kyolic or aged garlic extract allicin and polysulfides are absent. The key substance is S-allyl cysteine (See last section).

B lymphocytes respond to various stimuli by producing antibodies which help fight off many common infections [67]. The other 3 groups attack directly foreign invaders such as cancer cells, bacteria, viruses or fungi. Some carry out their attack by secreting powerful chemicals called cytokines; examples are interferons and interleukins. Lymphocytes circulate in blood and lymph but also can enter the tissues. They are broadly divided into B lymphocytes, T lymphocytes and null cells. All three types are small, motile, non phagocytic cells. Once stimulated with an antigen and appropriate cytokine/cellular signals the immune cells progress through the cell cycle and enlarge into a blast cell. Null cells are peripheral blood lymphocytes. They fails to express membrane molecules, 1 g or TcR or typical CD molecule. One functional population of these cells are the NK cells (Natural killer cells).

NK cells kill tumor cells or virally infected cells by direct membrane contact or through antibody dependant cell mediated cytotoxicity. These cells are activated by substances called interleukins and interferons. NK cells recognize infected cells especially those attacked by viral agencies and destroy them. They also have the ability to attack aberrant cells that could cause tumors [4].

Garlic principles attract immune cells to the site of injury [66]. Various nutritional medicines (neutraceuticals) function in a similar way and boost up the immune system. Viz; garlic, onions, ginger, turmeric, apple, pomegranate, mushrooms and various vegetables also contain such neutraceuticals as described earlier in a book [4] and these are called functional foods in their raw form. A group of researchers [68] showed the effect of raw garlic on the

action of NK cells of human volunteers. They selected 3 groups of volunteers for the experiment. The first group consumed 0.5 g/kg/bodyweight of crushed and cooked garlic every day for 3 weeks. The second group consumed 1.8 g kyolic (6 capsules of aged and odorless garlic extract from Japan) every day for 3 weeks. The 3rd group used no garlic and served as control.

After 3 weeks blood samples from each volunteer group were used to find their effects on tumor cells in laboratory culture. The NK cells from the samples of those who ate raw garlic killed 139% more tumor cells than those from control group. The NK cells of the kyolic garlic group killed 159% more tumor cells than those of the control group. The major ingredients in kyolic are S-allyl cysteine and cycloalliin. These compounds may have a better immune stimulating effect than those in crushed and cooked garlic viz; allicin and DADS or AMDS are all converted to dithiins and lesser active compounds on cooking. Kyolic is not heat treated and hence it is superior to cooked items.

Garlic Versus Stress and Immune System

There are many papers documenting that stress impairs our immune system, making it difficult for us to fight infection and even cancer [69–71]. Dr. Tohru Fuwa and associates [72–74] conducted three studies to unveil the beneficial effects of garlic against stress. Two of them are described here. In one study researchers randomly [72] divided mice into 3 groups. The first group was subjected to cold temperature (environmental stress), the second group was put in a box that was mounted on an oscillator that shook the box at 129 cycles/min for 4 h (physical stress). The third group was subjected to rope climbing (also a physical stress). Researchers noted that the stresses caused the mice to behave abnormally, all suffered motor coordination, extreme fatigue and loss of appetite. Half of the mice of all groups were then given garlic (high dose of kyolic liquid extract) and the experiment was repeated. Those who ate the kyolic were able to maintain motor coordination, recover partly from fatigue and function more efficiently than those who did not eat garlic. In another experiment [73] the researchers restrained the movements of a group of mice for 12 h a day for four consecutive days-an experiment designed to mimic the effect of psychological stress. At the end of the 4 days, the mice showed markedly reduced weight of spleen and thymus and markedly fewer B lymphocytes with which to fight infections. When part of the mice was supplemented with garlic extract no weight loss occurred and the optimum number of B lymphocytes was restored boosting the immune system [74]. This effect of garlic was mediated via a supply of energy (ATP) to the cells as suggested by Bogin [62] in his experiments. It is recorded that the Egyptians gave garlic containing diet to the labourers engaged in the construction of pyramids to sustain their energy [75].

In another study [76] conducted by Dr. Arun Bordia Rtd. cardiologist and others in RNT Medical college at Udaipur, India, they observed a positive effect of garlic oil on the physical endurance and adaptability in patients with coronary artery disease. The effect of 6 week garlic oil administration was observed on cardiac performance and exercise tolerance in 30 patients of coronary disease. After initial tread mill stress, they were administered garlic oil in the dose of four capsules (6 mg/capsule) twice a day for 6 weeks and tread mill test was repeated. Garlic oil significantly ($P < 0.01$) reduced the heart rate at peak exercise and also significantly reduced the work load upon the heart resulting in better exercise tolerance ($P < 0.05$) as compared to the initial test. Therefore garlic oil appear to be a good adaptogen to be utilized in CVD patients.

Cancer Preventive Effects

A metanalysis [25] that systematically reviewed human epidemiological studies of the relationship of garlic consumption and cancer shows that it reduces 30% colorectal and 50% stomach cancers with a trend towards reduction in prostate, breast and laryngeal cancers.

An epidemiological study [24] reported by Mei et al. from China showed that in Cangshan county areas where people regularly eat garlic (20 g/day) daily, suffered least from stomach cancer (3 in 100,000) as compared to a 13 fold increase in Qixia county areas where people used no garlic. (40 in 100,000). Further it was shown that Cangshan residents had lower concentrations of nitrites in their gastric juice than those in Qixia. Nitrites convert amines in our system or food to powerful carcinogens known as nitrosamines. Garlic principles may be protecting the system from nitrite accumulation [24, 65]. In a comparative study of effectiveness of garlic extract (kyolic) to treat cancer, it was found that it is significantly more active than BCG, a live vaccine used to treat that type of cancer [65, 77]. In another experiment [66] Lau suggested that garlic principles, ajoene and diallyl disulfide, detoxify carcinogens and protect the body from toxins like aflaloxin B1 and benzo (a) pyrene. It is also known that diallyl disulfide inhibits in vivo activation of nitrosamines. Unsaturated polysulfides found in allium principles inhibit tumor promotion [78–80] perhaps by enhancing glutathione—dependent detoxification enzymes. Injection of tumor cells treated with garlic extract, induced tumor immunity in mice. According to Block the antitumor effect of allicin is mediated by redox-sensitive signaling such as activation of P_{21}(ras) [81]. The antitumor effect of allicin is likely related to its immune stimulatory properties [82].

Garlic Principles Enhance Blood Fibrinolytic Activity

Reduced blood fibrinolytic activity (BFA) may promote thrombus formation in atherosclerotic vessels. Accordingly the greater the fibrinolytic activity the more favorable the antithrombic effect [83]. Gupta et al. [84] were the first to report that a fat induced decrease in BFA could be prevented by ingestion of fried onions. BFA was reduced by 23% ($P < 0.01$) 4 h after ingestion of a high fat diet in 20 healthy adult males. Addition of fried 60 g onion to meal of each person showed a 24% increase in BFA ($P < 0.01$). In older males also more or less similar results were obtained. Menon et al. [85] repeated this experiment in England involving 22 subjects and confirmed the beneficial effects of onion on BFA. Jain [86] also did this experiment with 50 healthy adults and got similar results. In 25 fasting subjects also onion ingestion increased BFA significantly ($P < 0.01$). Bordia [87] and Augusti [88] teams of researchers from India and UK respectively did similar experiments with feeding juices and extracted oils of garlic and onions and got encouraging results. The fibrinolytic activity of alliums was attributed to ajoene and polysulfides present in the essential oils of alliums by these workers. The latter group also reported a medium effect of cycloalliin, an imino acid isolated from onion. The advantage of the latter is that it is odourless and preferred to bad smelling oils. The doses of oils and cycloalliin were 0.125 g/person. Mechanism of action of fibrinolysis may be based on action of various sulfides in allium oils, i.e., exchange reactions between sulfides and fibrin clot. Alternatively oils may stimulate liberation of plasminogen activator from blood vessels. This needs further experiments to clarify the mechanisms. Bordia et al. [89] investigated on the effects of feeding essential oil of garlic obtained from 1 g raw garlic/kg body wt in ten healthy adults for 3 months. Their BFA increased by 130% over the initial level. On discontinuation of garlic oil feeding these values returned to normal after 2 months. BFA increased by 63 and 95.5% in ten acute MI patients [90] who consumed raw garlic for 3 months. These values returned to initial levels after discontinuation of garlic for 30 days. Chutani and Bordia [91] also studied the effect of fried or raw garlic (0.5 g/kg body wt) on BFA in 20 patients with a history of MI. Both samples increased the BFA by 63–72% after 6 1/2 and 12 h periods. This experiment was later repeated in 30 ischemic heart disease patients over a 6 weeks period. Here also their BFA increased by 85% in 1 month's time and returned to initial values after discontinuation for 2 weeks.

Synthetically prepared cycloalliin was tested by Agarwal et al. [92] on ten healthy subjects and 8 patients with MI. Dose was 0.25 g in a capsule. BFA was increased significantly as compared to controls ($P < 0.001$) in test groups. S-methyl cysteine sulfoxide gets converted to cyclic imino acid (cycloalliin) during isolation in an alkaline medium.

Antidote for Heavy Metal Poisoning and Other Toxins

According to Petkov [93] the sulfides of garlic are useful as antidotes for 'saturnism' chronic lead poisoning. In a clinical study garlic was given to workers in a lead mine who suffered from lead intoxication. It was found that the symptoms of poisoning were considerably diminished by this treatment. Garlic and onion juice have similar effect on lead toxicity [94, 95]. The toxic effects of arsenic in mice have also been shown to be significantly reduced by feeding the animals with aqueous garlic extract [96, 97]. Petkov and Kushev [98] investigated the influence of garlic juice on the excretion of ^{198}Au (radioactive gold) in rats. It was shown that garlic accelerated the excretion of the radioactive isotope of gold and decreased its accumulation in various organs. Garlic also showed good protective effects against experimental intoxication with Cd and Hg and organo metallic compounds according to various workers [75]. The authors of this paper also showed the beneficial effects of garlic oil and onion oil in ameliorating the toxic effects of lead acetate in the drinking water of rats [6]. These oils helped to remove lead salt from the blood of the rats fed with lead acetate along with and without alcohol. They helped to prevent lipid peroxidation and deterioration of Hb, serum proteins and enzyme activity. Viz, catalase. AST and ALT activities. Their body lipids were raised and vitamin C level in serum was significantly lowered. Simultaneous administration of allium oils along with lead salt/alcohol through drinking water significantly ameliorated the bad effects of lead salt/ethanol. Lead acetate solution (160 mg/l) or 10% alcohol by volume was given in drinking bottles ad libitum for a month. Simultaneously G.O/O.O or vitamin E was administered through a stomach tube to different test groups of lead salt with and without alcohol. Dose of oils and Vit E was 100 mg/kg/day. Control groups were also set up in the experiment. After 1 month feeding all the groups were sacrificed and their blood and tissue parameters were analyzed. Vitamin C and E levels in serum of test groups were significantly raised as the oils spared the destruction of the vitamins. All the tissue and blood parameters said above were also protected by the oil and vitamin E feeding and blood level of lead was normalized. All these results highlight the metal detoxifying effects of vitamin E and allium oils. The allium oils showed comparable effects with vitamin E, a standard antioxidant. It is assumed that lead was removed from the blood stream as PbS by the polysulfides present in allium oils. The detoxifying effects of vitamin E, G.O and O.O are related to the activity of certain enzymes involved

in biotransformation of xenobiotic agents, especially glutathione-S-transferase in the liver. Huh et al. [99] demonstrated in rats that the hepatic GSH—S-transferase is greatly enhanced by the simultaneous injections of diallyl disulfide (DADS) at varying doses (80–160 mg/kg/day) for 3 days. The microsomal enzymes and serum transaminases are not affected. The removal of Cu^{2+}, Pb^{2+}, Al^{3+} and Hg^{3+} from their solution was showed by Lau [65] on addition of a liquid extract of garlic (Kyolic). The above salt solutions lyse red blood cells which could be prevented if 0.05 ml solution of 1:10 diluted kyolic is added in test tubes containing 15 ml of a 5% suspension of human RBC and different heavy metal salt solutions.

Antidiabetic Effects

In 1924 Mahler and Pasterny [100] conducted a clinical experiment with two diabetic patients and the result was surprisingly positive. They received 10–15 g fresh garlic sliced and distributed into three portions over the day. Urine sugar excretion was reduced from 3.2 to 1% in one case and 3.8% to zero in the other case. Blood sugar decreased correspondingly. Janot and Laurin [101] confirmed the hypoglycemic action of onion in rabbits. They injected alcoholic extract of onions subcutaneously into rabbits. Their blood sugar level fell down within 1–2 days. Later Laland and Havrevold [102] isolated a hypoglycemic fraction from garlic and confirmed its action in rabbits and pancreatectomized dogs. The hypoglycemic principles in onion and garlic were found to be diethyl ether soluble fractions of the dried powdered samples and they showed 58–76% activity of tolbutamide for a dose of 0.25 g/kg body wt in normal rabbits [103, 104]. Augusti and Mathew [105] isolated allicin from garlic and demonstrated its hypoglycemic effect in alloxan diabetic rabbits. Serum insulin level was also increased in the rabbits. Feeding of allicin and tolbutamide to separate groups of alloxan diabetic rats (0.25 g/kg) increased their liver glycogen with in 6 h and the values were 26 and 18% respectively over the control. Hypoglycemic action of the etherial oil of garlic or garlic extract was demonstrated in alloxan diabetic rats by Jain and Vyas in 1975, Devaki et al. in 1992, Chang and Johnson in 1980 and many others as reviewed by Reuter et al. [106]. Antidiabetic action of S-methyl cysteine sulfoxide isolated from onions [107] and S-allyl cysteine sulfoxide isolated from garlic [108] also was showed by Augusti's team. Both the allium oils and the above sulfoxide amino acids are hypoglycemic agents because they are insulin secretagogues as well [21, 109, 110].

Alliums could Give Protection Against Radiation

Lau and associates [65] conducted an experiment to determine whether garlic could provide protection against radiation. They incubated human lymphocytes in tissue cultures for 2 h both with and without kyolic (2.5 mg/ml) or fresh garlic extract (also 2.5 mg/ml). They also set up tests using L-Cysteine (1 mg/ml) a compound known to protect against radio activity. They then irradiated all but one of each set of cultures with 2,000 rads from a Therac 20 linear accelerator and each unradiated culture served as control. They then tested viability of the cells with trypan blue dye 3, 24, 48 and 72 h following irradiation. The unirradiated lymphocytes remained viable in the tissue culture during the 72 h observation. Irradiated control cultures not infused with protection agents steadly declined; within 72 h only 25% of the cells were still viable. Cells incubated with L-cysteine or Kyolic enjoyed significant protection; a few cells died with in the initial few minutes, but almost all others were viable at the end of the test period. Surprisingly, the fresh garlic extract proved extremely toxic to the lymphocytes. None survived beyond 24 h. The reason may be that the prooxident allicin in fresh garlic extract might have destroyed the lymphocytes where as in aged kyolic sample allicin is absent as it was converted to ajoene and various polysulfides. Therefore polysulfides and cysteine gave protection to lymphocytes from radiation possibly through a repair mechanism applying free radical scavenging of the irradiation products in the culture viz; break down products of water i.e. $OH^{\bullet}$ and $H^{\bullet}$. Free radicals oxidize cells and destroy them. This is prevented by scavenging them by cysteine and polysulfides.

$$2RSH + 2OH^{\bullet} \rightarrow R-S-S-R + 2H_2O$$
$$R-S-S-R + 2H^{\bullet} \rightarrow 2RSH$$
$$R-S-S-R + 2OH^{\bullet} \rightarrow 2RSOH$$

Antiaging Effects

Aging is related to the overproduction of free radicals in the body and a lack of the capacity of the body to scavenge them and repair the cells. Moreover the destruction of receptors in various cells and neurons may also quicken the aging process in the body. Antioxidants may help to slow down aging in the body. In this regard garlic has a role [83]. Svendsen et al. [111] used Hayflick system of cellular aging for testing the effects of aqueous extracts of garlic on long term growth characteristics, cellular morphology and DNA, RNA and protein synthesis of normal diploid human skin fibroblasts. They used normal and cancerous skin fibroblasts for study in a culture medium. The results show that garlic extract (250 μg/ml) acts as a growth suppressor for potentially immortal, cancerous and rapidly dividing cells owing to the increased sensitivity of such cells to garlic principles. Normal human skin fibroblasts grown in the presence of 100 and 250 μg/ml garlic extract could be specially passaged for 55–66 PDS (population doublings)

in about 475 days before they die. This is the first experiment in which an external agent prolonged the life span of cells to such an extent. The final cumulative population doubling levels (CPDLS) were 56 ± 3 for untreated control cells and 60 ± 3 for cells treated with 100 μg/ml and 57 ± 3 for cells treated with 250 μg/ml garlic extract throughout their lifespan. Therefore in terms of the effects of garlic principles on the maximum proliferative capacity and life span of cells, along term treatment of cells with 100 μg/ml garlic extract increased cellular life span slightly only. In comparison none of the cancerous immortal cells could be grown for such a long duration in the presence of garlic. A comparison of long term longevity curves of normal human cells with and without a treatment (with 100 μg/ml) shows a tendency of certain antiaging effects. Further evidence that certain doses of garlic treatment have some anti aging effects on human cell is obtained by comparing the average P.D. times of treated and untreated cells. The PD rate was less for the untreated and more for the treated cells that is 3 days (more time) and 2 days (less time) respectively and the life span was less for the untreated than the treated cells. Further the average number of cell yield per flask was less for the untreated than the treated. Garlic treatment maintained a relatively youthful morphology of the skin firoblasts at comparable CPDLS between treated and untreated groups. In cell culture the researchers showed that 100 μg/ml garlic extract treated cells at CDPL 17 stage appeared much healthier and better arranged in fingerprint patterns than the controls of similar CDPL. Further treated cells at CDPL 50 stage looked comparatively much healthier and spindle shaped than controls of CDPL 46. These results illustrate the antiaging effects of garlic extract in general. In conclusion these results high light the dual role of garlic extract as to suppress the growth of potentially abnormal cells as well as to give beneficial effects to maintain normal cells in a very healthy pattern of growth and long term span of life. Their mechanism of action is dependent on free radical scavenging and enhancement of endogenous enzymes like SOD, catalase, glutathione reductase, glutathione S-transferase etc. as described earlier in our papers [4–6, 19–21, 34–37]. These results answers the doubts raised by Singh et al. [1] as to the effects of AOs on endogenous enzymes.

Effects on Enzymes

Wills [112] tested the effects of allicin on a total of 28 different enzymes. He demonstrated that strong inhibitions occurs on thiol group enzymes e.g.; Succinate DH, Xanthine oxidase, Hexokinase, cholinesterase, triose phosphate dehydrogenase, LDH, tyrosinase, ALP etc. Unlike allicin the diallyldisulfide and other polysulfides and diallyl sulfoxide have no inhibitory effect on the enzymes and therefore unstable allicin is not a long standing garlic principle that could harm the body anyway. Garlic oil influences oxidative phosphorylation in liver mitochondria of mice. The extent of inhibition of respiration depends on the respective substrate. Inhibition of oxidation of NAD dependent substrates such as glutamate is stronger than that of succinate or ascorbate. DADS has an effect similar to garlic oil but the effect of DPDS is much smaller [113].

According the Bogin [62] garlic extract acted as an uncoupler (most probably due to allicin) of oxidative phosphorylation, inhibited the oxidation of succinate by 50% and increased the activity of mitochondrial ATP ase by 100%, the membrane became clearly more permeable to certain substrates (e.g.; ATP) and sensitive to hypotonic solution. These actions of allicin and garlic oil explain the stress tolerance of animals and people who consume garlic diet. However if the amount of garlic extract or oil is limited it may not create problems as the components have other multifarious functionary roles that could improve the health. A change in the activity of certain liver enzymes has been observed in vivo after administration of allicin (100 m/kg/day) to normal rats for 15 days by the senior author's team [31]. This may give some explanation for the benefits of garlic principles. Liver enzymes lipase and phosphorylase increased significantly while the activity of glucose—6—phosphatase was decreased. The lipid lowering activity and supply of glucose and ATP to the tissues by the action of garlic principles consumed by animals may be answered by these results. This may be due to secretion of insulin also [21, 34]. Allicin for a short time and its transformed forms of ajoene and polysulfides for a long term exhibit these actions. They may decrease blood glucose and lipids and increase liver glycogen level in diabetic animals [31, 105]. Sulfoxide aminoacids SMCS and SACS of onion and garlic also showed similar actions in diabetic rats along with an increase in the level of serum proteins [114]. Garlic oil polysulfide oxides interact with SH group albumins in serum which inactivate insulin and also with thiol group enzymes such as HMGCOA reductase and fatty acid synthase thus limiting the serum levels of cholesterol and FFA in serum and tissues [19, 20, 42, 105]. Garlic and onion oils and their sulfoxide aminoacids increase the activities of SOD, catalase and glutathione reductase and GSH content in the tissues also [20, 34, 115]. These aspects of reaction of the above oils were discussed in the section on their antioxidant role. Garlic oil and its sulfides (DADS, DATS) and bis (1-propenyl) sulfide are potent inducers of the phase II enzymes for carcinogens viz; quinone reductase, glutathione reductase and S-transferse [116–118]. Thus the activation or induction of various enzymes are possible by garlic compounds.

The Advantages and Limitations of Aged Garlic Extract (AGE) and Garlic Powders

Alcoholic extract of sliced garlic in 15–20% ethanol when stored for 20 months followed by filtration and concentration is called aged garlic and it is marketed in Japan with the name Kyolic [67]. In this extract only traces of ajoene and polysulfides are formed and they are evaporated off unless stored with tight lids. The key substance in it is S-allyl cysteine with some amount of cycloalliin. As the garlic is not ground initially alliinase action is lost and the precursor sulfoxide amino acids are not converted to allicin and its transformed products [119]. Kyolic is an odourless sample of garlic extract as it is devoid of garlic oil or its polysulfides. Therefore medicinally it is less active than garlic oil. Cycloalliin is a cyclic formation of S-methyl cysteine sulfoxide and S-allyl cysteine is a hydrolytic product of γ-glutamyl—S-allyl cysteine [21, 88, 106]. Most of the research on AGE has been conducted in the areas of anticancer effects, immune effects, cardiovascular effects and stress relief [65, 106]. Reasonable doses in humans have been reported to result in relief of fatigue, depression, various complaints and recovery from cancer therapies [120–123]. Kyolic or Kyolepin has the limitation that the extract contains only 1/10th sulfur compounds of crushed garlic and its effects are very mild and every sample may not be of equal potency.[106]

Odorless Garlic Powder

A dry powdered extract of garlic is a later discovery to avoid the obnoxious smell of garlic and its extract. For this raw garlic bulbs are irradiated with microwaves to inactivate the action of the enzyme alliinase that produces allicin. After wards the above sample is deep frozen, crushed and extracted with aqueous alcohol. Later alcohol is removed under reduced pressure and the residue is lyophilized [106, 124]. The extract contains all original sulfur compounds of garlic viz; Alliins (SACS, SMCS) and γ-glutamyl–S-allyl cysteinyl peptides. The final product is marketed as tablets; Garlic powder is superior in action to aged garlic extract (AGE).

Comparison of the Effects of Garlic Powder with AGE on Cardiovascular Patients

A study on the short term effect on peripheral capillary blood in volunteers after consumption of four capsules of AGE(2.8 g/person) revealed no change in plasma viscosity, erythrocyte flow rate, hematocrit or fibrinogen content, while consumption of 900 mg of garlic powder tablets produced significant improvements in all four parameters [125]. However in a study on serum lipids when 4 ml liquid AGE/day (1 g kyolic) was given to hyperlipidemic patients for 6 months [65], significant fall in serum lipids was found only after 2–3 months. During the initial period there was a rise in the level of lipids viz; total cholesterol, LDL cholesterol and TGs due to mobilization of body lipids, says the researcher Lau. HDL cholesterol fell from the initial period of treatment while LDLc increased till the 2nd month and then fell down later significantly.

Next to the allicin, alliins (SACS/SMCS) could be the strong lipid lowering agents as has been indicated when fed to rats at the high level of 1% of the diet by Itokawa et al. [126] for 2 weeks or at a high dose of 200 mg/kg by senior author's group [108, 127] for 2 months. In contrast to 3–4 months needed for the AGE to lower blood lipids, other studies with garlic cloves and standardized garlic powder tablets have shown significant decreases in 1–2 months [106] .

The differences between the two types of garlic products may be due to the low contents of organic sulfides with alkyl or alkenyl groups in AGE as compared to garlic powder. Therefore the potencies of garlic preparations are in the order:

Garlic oil > Garlic powder > Aged garlic (e.g.; Kyolic).

Toxicity of Garlic and Onion Compounds

Prolonged or excessive intake of allium species may interfere with Hb production and may lead to red blood lysis. This is because cysteine shall be inactivated by the disulfide of allicin/of allium principles and this may prevent the availability of cysteine for globin synthesis [21]. Prolonged feeding of raw garlic/onions to rats has resulted in anemia, weight loss and failure to grow. Joseph described this to the toxicity of acrolein (CH_2=CHCHO) production from allicin [4]. Some people have an allergic response e.g.; dermatitis or asthma to fresh garlic or onions. The beneficial as well as harmful (if excess is used) effects of allicin products are due to the actions of allicin, ajoene and polysulfides of alliums on thiol group enzymes and SH group- proteins and cysteine of the body. If they are used viz; 5 g garlic, 10 g onion or their equivalent of kyolic or garlic powder capsules daily for 3 days per week with good amount of milk, fish and other protein rich diet their beneficial effects can be experienced without any harm. Alternatively to control any disease Viz; CVD, inflammation, hyperlipidemia, diabetes, viral infection etc. the above items and their oils can be used according to the prescription of a doctor for a specific period. In country side it is a practice to give a diet of ground onions and palm sugar to bulls in rainy seasons to strengthen their body and purify blood. In conclusion we can say garlic, onion and their products can serve as ideal antioxidants as well as drug or drugs with multifunctional activities to prevent or cure

various diseases. If used in limited quantities as an additive to our food (ground garlic contains the maximum useful nutraceutucals) as was the practices of our ancestors, alliums may protect our body from many ailments including that due to heavy metal toxicity. They can be used in chutney or in salad as the Punjabies do for their health. According to Dr. Arun Bordia garlic is "spice of life" if used wisely.

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