Antioxidant and drug metabolism

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The production of physiological amount of free radical is essential to fight against an unfavorable environment. The free radicals like nitric oxide (NO), superoxide anion, and related reactive oxygen species (ROS) play an important role as regulatory mediators in signaling processes. In higher organisms, NO and ROS regulates vascular tone, oxygen tension in control of ventilation and erythropoietin production.[1] Free radicals activate a signal transduction from membrane receptors, for example ROS is essential for tissue factor protein expression in endothelial cells, TNF-γ-induced vascular cell adhesion protein 1 (VCAM-1) in vascular smooth muscle cells (VSMCs), tyrosine phosphorylation in fibroblasts and lymphocytes, etc. Similarly reactive nitrogen species (RNS) is important in norepinephrine-induced prostacycline release in hypothalamus, formations of synaptic connections in olfactory receptor neurons, N-methyl-D-aspartic acid (NMDA) receptor activity in cortical neurons, etc.[2]

Antioxidants are substance witch scavenge the free radical for maintaining the cellular and systemic health. There is a dynamic balance between the amount of free radicals produced and the antioxidants to eliminate them from the body. The antioxidants (vitamin C, vitamin E, etc) and antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidases) act synergistically in scavenging free radicals[3] that may inhibit the free radicals functions and alter the pharmacokinetics of the pharmaceuticals.

Antioxidants do have a role in the pharmacokinetics of drugs. They can enhance or decrease the drug absorption leads to altered drug response. The effects of drugs are modulated by their rates of metabolism by the liver.

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Metabolism of drug occurs in two processess *viz.,* phase I and phase II reactions. The cytochrome P450 (CYP) system family of enzymes present in liver, kidney, intestinal mucosa and other tissues. They predominantly catalyze oxidation, reduction, and hydrolysis reactions, which increase polarity of lipophilic compounds. These interactions involved the inhibition or induction of metabolizing enzymes and efflux transporters, resulting in altered systemic exposure and adverse drug reactions or loss of efficacy. Although 12 gene families have been identified, three categories of these enzymes are of the greatest significance in humans: CYP 2C, CYP 2D6, and CYP 3A4.[4,5] CYP 2C (particularly 2C9 and 2C19) is responsible for the metabolism of many anticonvulsants, proton pump inhibitors, antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Flavonoids are polyphenolic compounds rich in antioxidants and good sources of flavonoids include all citrus fruits (quercitrin), berries, ginkgo biloba, onions and tea. Flavonoid can activate or inhibit P450 enzymes (CYP3A4 and CYP1A2). Interactions of flavonoids with these enzymes may enhance or inhibit their actions. The flavonoids in grapefruit juice (naringin, naringenin, limonin, obacunone) inhibit CYP3A, as measured by 6b-hydroxylation of testosterone by rat and human liver microsomes.[6] Quercetin and kaempferol in grapefruit may also inhibit metabolism of midazolam and quinidine by inhibiting CYP3A4.[7]

The antioxidants containing food sources like citrus fruits, grapefruit juice and myricetin are extend the pharmacokinetic of the most of the drugs. Myricetin inhibited CYP3A4 and CYP2C9 enzyme activity and enhance the pharmacokinetic of losartan by 30–50%. Myricetin 2/8 mg/kg increased the area under the plasma concentration–time curve of losartan by 31.4–61.1% and peak plasma concentration of losartan by 31.8–50.2%, as a result the absolute bioavailability of losartan increased significantly and the metabolite–parent area under the

plasma concentration–time curve ratio decreased by 20% when compared with the control.[8] In healthy volunteer grape juice does not have any significant alteration in pharmacokinetic parameters of quinidine, but the maximum concentration (t_{max}) was obtained by grapefruit juice and area under the curve (AUC) reduced by 33% by grapefruit juice.[9] The extended pharmacokinetic of drugs on repeated dose administration leads to cause of adverse drug reaction.

Grapefruit juice consumption increased bioavailability of drugs by inhibiting intestinal cytochrome P450 (CYP) 3A4, but not hepatic CYP3A4 or colon CYP3A5,[10] this may lead to develop an adverse event when continues an administration of the pharmaceuticals. Some of the clinical trial suggested that, the antioxidant does not have any effect on energy metabolism and oxygen uptake.[11] Supplementation of antioxidants may be beneficial to health in disease condition to neutralize the free radicals. But when administering them along with drugs should be taken care of pharmacokinetics of drugs. So the type and optimization of administration of antioxidant in clinical condition is essential for recommending them as supplements.

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