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بالرسالة صفحات

لم ترد بالأصل

HOSSAM MAGHRABY

COMPARATIVE STUDY BETWEEN THE EFFECT OF SOME HEPATIC PROTECTOR DRUGS ON PROGNOSIS OF HEPATIC DISORDERS.

Thesis
presented by

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in partial fulfilment of
Ph.D. Degree in Pharmacology

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بسم الله الرحمن الرحيم

"ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدا"

صدق الله العظيم

الكهف (١٠)

To My Family

The Soul Of My Life

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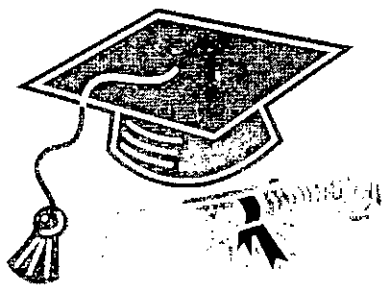


PREFACE

PREFACE

It is emphasized that oxidative damage could be a consequence of tissue injury or as a cause of it (Halliwell,1994).

The generation of reactive free radicals reduce the antioxidant defenses in the liver through stimulation of lipid peroxidation which has been implicated in a wide variety of hepatic injuries and diseases (Ross & Moldeus,1991).

A great deal of interest focuses on the mechanisms whereby the antioxidant agents can prevent or decrease the potentially harmful radical reactions (Sies & Krinsky,1995).

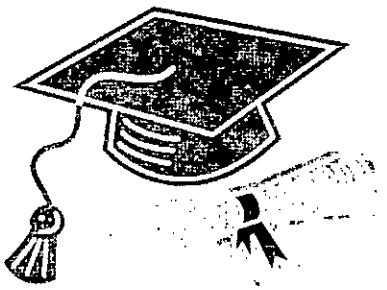
Vitamin E (Reynolds,1996 b*) , vitamin A (Cahill et al.,1993) , and silymarin (Flora et al.,1998) are considered to have antioxidant activity , thus may play a valuable role in cellular defense in the liver.

Hopefully , this realization will contribute to the development of new preventive and therapeutic strategies of liver disorders (Halliwell,1994).

A particular area of interest in pharmacology is the possibility that the side effects of several drugs involve increased oxidative damage (Aust et al.,1993).

Drug-induced hepatotoxicity , e.g. acetaminophen , is shown to increase lipid peroxidation (Reiter & Wendel,1983).

Also , hepatic schistosomiasis causes damage and fibrosis of the liver by an oxidative mechanisms (Pincus et al.,1981 and Bissell et al.,1990).



REVIEW OF LITERATURE

FREE RADICALS

Free radical can be defined as any highly reactive molecular species capable of independent existence that contains one or more unpaired electrons (i.e. one electron is alone in an orbital) (Halliwell,1991 ; Halliwell et al.,1992 and Ward & Peters, 1995).

The reactivity of these molecules results from the fact that more energy is required to maintain two separate species each with an unpaired electron , than to allow them to come together and share electrons.Thus the reactivity of a free radical is inversely related to its stability (Aitken & Fisher,1994).

It is noted that free radicals may be anionic (negatively) , cationic (positively) charged or electrically neutral (Slater,1984 ; Ward & Peters,1995 and Punchard & Kelly,1996).

The presence of the unpaired electron in the free radical is conventionally represented by a superscript bold dot (e.g. $R^{\cdot}$) (Slater,1984).

Formation And Sources Of Free Radicals :

Free radicals can be formed by three different mechanisms: first ,by homolytic cleavage of a covalent bond of a normal molecule with each fragment retaining one of the unpaired electrons to yield a neutral radical ($R\text{-}R \longrightarrow R^{\cdot} + R^{\cdot}$) ; second , by the addition of a single electron to a normal molecule i.e. one electron "reduction" or "electron transfer " to yield an anion radical ($R + e^{-} \longrightarrow R^{\cdot -}$) ; third , by loss of a single electron from a normal molecule i.e. one electron "oxidation" to yield a cation radical ($R \longrightarrow R^{\cdot +} + e^{-}$) (Cheeseman & Slater,1993 and Dahm & Jones, 1996).

In biological systems , electron transfer mechanism is more common than homolytic fission (=cleavage) , which generally requires high energy input from either high temperature , U.V. light or ionizing radiation (Cheeseman & Slater,1993).

Free radicals are continuously generated by normal metabolic pathways as physiological process (Winklhofer-Roob,1994), where their formation in the living organism is considered essential for maintenance of the normal physiological conditions (Dowrschak et al. ,1990).

The reactive metabolites produced include electrophiles and free radicals , where "electrophiles" are the molecules containing positive center can react with cellular "nucleophiles" molecules that containing negative center e.g. glutathione , proteins and nucleic acids (Levi,1997).

Free radicals are produced mainly within the aerobic cells (Kalra et al., 1994). The endogenous sites of free radical generation include all cellular constituents including , mitochondria , lysosomes , peroxisomes , endoplasmic reticulum and plasma membranes as well as sites within the cytosol (Machlin & Bendich ,1987).

The **"endogenous sources"** of free radicals include :

(1) Respiratory Burst :

During cellular host defense system (including neutrophiles , monocytes, , eosinophiles and macrophages) against parasitic infestation or inflammatory conditions , cause its protective role by a metabolic event known as "Respiratory burst" (Ward & Peters,1995). This process involves releasing amounts of reactive oxygen species including superoxide anion ($O_2^{\cdot -}$) , hydrogen peroxide (H_2O_2) , hydroxyl radical ($HO^{\cdot}$) as well as hypochlorous acid (HOCL) (Halliwell & Cutteridge,1984 and Winklhofer-Roob,1994).

Neutrophiles contain the enzyme myeloperoxidase which uses hydrogen peroxide (H_2O_2) to oxidize chloride ion (CL^-) into hypochlorous acid (HOCL) which is not only a powerful antibacterial agent , but also contributes to tissue damage (Halliwell,1991 and Halliwell,1995). This radicals are important in allowing the bactericidal effect of phagocytes to kill some of bacterial strains that they engulf (Curnutte & Babior,1987 and Halliwell,1991).

(2) Eicosanoid Metabolism :

During the formation of prostaglandin (PGG_2) from arachidonic acid , a trace of hydroperoxide is required to react with Fe^{3+} heme at the active site of cyclooxygenase enzyme to form a peroxyl radical that starts the chain propagating reaction of lipid peroxidation (Ward & Peters,1995).

(3) Endothelium – Derived Relaxing Factor (EDRF) Formation :

EDRF has now been identified as nitric oxide (NO) . The endothelium seems to produce continuously small amounts of superoxide which can react with nitric oxide (both are free radicals) to form nitrate ions (a non – radical product). Nitric oxide is also produced by macrophages and within neuronal cells in the brain (Ward & Peters,1995).

(4) Controlled Leakage In Enzymatic Reactions :

Free radicals , within the cell , can be derived from inevitable leakage of superoxide anions from the mitochondrial electron transport chain . Also , free radicals may be generated during the metabolism of various agents by cytochrome P-450 microsomal system . In addition , some enzymes are known to catalyze formation of free radicals e.g. xanthine oxidase (Ward & Peters,1995).