

**KESAN VITAMIN E DAN STEROID KE ATAS ENZIM PENANDA
DAN DETOKSIFIKASI PADA PLASMA DAN HEPAR
TIKUS TERARUH BARAH.**

ASMAH RAHMAT

**TESIS YANG DIKEMUKAKAN UNTUK MEMPEROLEHI IJAZAH
DOKTOR FALSAFAH**



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PENGAKUAN

Saya akui karya ini adalah hasil kerja saya sendiri kecuali nukilan dan ringkasan yang tiap-tiap satunya telah saya jelaskan sumbernya.

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Asmah Rahmat
ASMAH BTE RAHMAT
A1536

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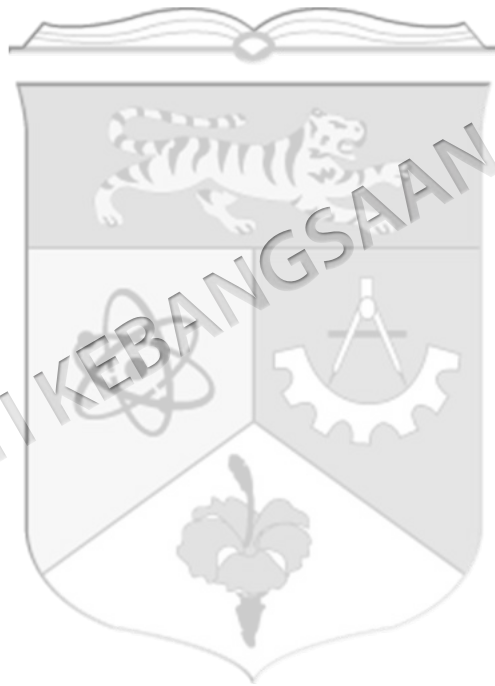
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ABSTRAK

Kesan vitamin E (tokotrienol dan tokoferol) dan steroid ke atas enzim penanda gamma-glutamil transpeptidase (GGT) dan glutathion S-transferase (GST) serta enzim detoksikasi lain pada tikus yang diaruh barah oleh dietilnitrosamin (DEN) dan 2-asetilaminofluoren (AAF) telah dikaji. DEN/AAF meningkatkan aras glutathion (GSH), GGT dan alkalin fosfatase (ALP) plasma dan UDP-glukuronil transferase (UDPGT), GST dan glutathion peroksidase (GPx) hepar. Suplementasi vitamin E kepada tikus perlakuan DEN/AAF menurunkan GGT, ALP dan GST kepada aras di antara kawalan dengan DEN/AAF. Tokotrienol atau tokoferol tidak memberi kesan kepada parameter yang diukur. Dos vitamin E yang berbeza (30, 60 dan 150mg tokotrienol/kg diet) menunjukkan kesan perlindungan yang ketara kecuali dos 15mg tokotrienol/kg diet. Kesan tokotrienol sebanding dengan tokoferol. Perlakuan DEN/AAF jangka masa panjang meningkatkan GSH dan kesemua enzim. Suplementasi tokotrienol (30 mg/kg diet) menurunkan aktiviti enzim di antara kawalan dengan perlakuan DEN/AAF. Aktiviti GPx dengan substrat hidrogen peroksid (H_2O_2) menurun seperti kawalan, GPx dengan substrat kumen hidroperoksid ($CuOOH$) tidak berubah dan glutathion reduktase (GRx) serupa DEN/AAF. Suntikan Estradiol (E_2) sahaja atau E_2 dan DEN/AAF meningkatkan GGT, UDPGT, ALP, GST dengan substrat 1,2-dikloro-4-nitrobenzen (DCNB) dan GPx (H_2O_2). Penambahan tokotrienol kepada DEN/AAF/ E_2 tidak memberi kesan kerana hanya menurunkan ALP sahaja. Walaupun suntikan progesteron atau DEN/AAF/progesteron meningkatkan UDPGT, ALP, GSH hepar, GST (DCNB) dan GPx($CuOOH$) tetapi GSH plasma menurun selepas 8 minggu. Penambahan tokotrienol kepada DEN/AAF/progesteron meningkatkan GGT plasma selepas 8 minggu di antara DEN/AAF dengan kawalan. Suntikan testosteron meningkatkan UDPGT dan GST (DCNB) sementara ALP meningkat di antara DEN/AAF dengan kawalan. GGT plasma meningkat di antara DEN/AAF dengan kawalan pada perlakuan DEN/AAF/testosteron. Penambahan tokotrienol menurunkan GGT plasma dan menurunkan lagi GPx($CuOOH$) daripada nilai kawalan. Suntikan Dexamethasone (Dex) meningkatkan kesemua enzim kecuali UDPGT, ALP (8 minggu) dan GST (DCNB). DEN/AAF/Dex meningkatkan kesemua enzim kecuali GST (DCNB) lapan minggu dan GPx. GGT dan GPx tidak dipengaruhi oleh penambahan tokotrienol kepada DEN/AAF/Dex, sedangkan enzim yang lain meningkat. Kesimpulannya tokotrienol dan tokoferol mengurangkan keterukan hepatokarsinogenesis yang diaruh oleh DEN/AAF. Tokotrienol kurang berkesan untuk perlakuan E_2 berbanding dengan steroid lain.

EFFECT OF VITAMIN E AND STEROIDS ON MARKER AND DETOXIFICATION ENZYMES IN THE LIVER AND PLASMA OF RATS TREATED WITH CARCINOGEN

ABSTRACT

The effect of vitamin E (tocotrienol and tocopherol) and steroids on the marker enzymes, gamma-glutamyl transpeptidase (GGT) and glutathione S-transferase (GST) and other detoxification enzymes in rats treated with diethylnitrosamine (DEN) and 2-acetylaminofluorene (AAF) were studied. DEN/AAF increased glutathione (GSH) and plasma GGT and alkaline phosphatase (ALP) as well as liver UDP-glucuronyl transferase (UDPGT), GST and glutathione peroxidase (GPx). Supplementation with vitamin E to rats treated with DEN/AAF reduced the GGT, ALP and GST to a value between control and DEN/AAF. Tocotrienol or tocopherol did not affect the enzyme activities. The different doses of vitamin E (30, 60 and 150mg tocotrienol/kg food) used showed protective effects except for the dose of 15mg tocotrienol/kg food. The effect seen with tocotrienol was similar to that of tocopherol. In the long term study, DEN/AAF also caused the enzymes to increase. Supplementation of tocotrienol (30mg/kg diet) again decreased these parameters to values between normal and DEN/AAF except for GPx with hydrogen peroxide (H_2O_2) as substrate, GPx with cumene hydroperoxide (CuOOH) as substrate and glutathione reductase (GRx). Injection of Estradiol(E_2) only or E_2 to DEN/AAF treated rats increased GGT, UDPGT, ALP, GST with 1,2-dichloro-4-nitrobenzene as substrate (DCNB) and GPx (H_2O_2) which were unchanged with tocotrienol supplementation. Although injection of progesterone or DEN/AAF/progesterone increased UDPGT, ALP, liver GSH, GST (DCNB) and GPx (CuOOH), the plasma GGT decreased after 8 weeks. Supplementation of tocotrienol to DEN/AAF/progesterone for 8 weeks decreased the plasma GGT. Injection of testosterone increased UDPGT, GST (DCNB), ALP and plasma GGT to values between control and DEN/AAF. Supplementation of tocotrienol decreased plasma GGT and GPx (CuOOH) to below control values. Injection of Dexamethasone (Dex) increased all the enzymes except UDPGT, ALP (8 weeks) and GST (DCNB). DEN/AAF/Dex increased all enzymes except GST (DCNB) (8 weeks) and GPx. Whilst GGT and GPx were unaffected by the tocotrienol supplementation to DEN/AAF/Dex, the other enzyme increased. In conclusion, tocotrienol and tocopherol reduced the severity of hepatocarcinogenesis induced by DEN/AAF. Tocotrienol was less effective when E_2 was given compared to the other steroids.

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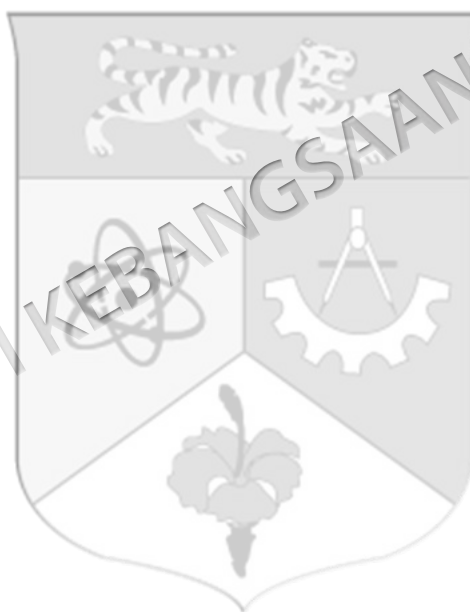
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SENARAI SINGKATAN

AAF ; 2-asetilaminofluoren

ALP ; alkalin fosfatase

ATP ; Adenosin trifosfat

DEN ; dietilnitrosamin

Dex ; Dexamethasone

E ; vitamin E

E₂ ; estradiol

EE₂ ; etinil estradiol

GGT ; gamma-glutamil transpeptidase

GSH ; glutathion

GSSG ; glutathion bentuk teroksidasi

GST ; glutathion S-transferase

GST(CDNB) ; glutathion S-transferase dengan 1-kloro-2, 4-dinitrobenzen sebagai substrat kedua.

GST(DCNB) ; glutathion S-transferase dengan 1,2,-dikloro-4-nitrobenzen sebagai substrat kedua.

GPx ; glutathion peroksidase

GPx(CuOOH) ; glutathion peroksidase dengan kumen hidroperoksid sebagai substrat.

GPx(H₂O₂) ; glutathion peroksidase dengan hidrogen peroksid sebagai substrat.

NADPH; Nikotinamid adenin dinukleotid fosfat bentuk terturun.

UDPGT ; UDP-glukuronil transferase

BAB I

PENDAHULUAN

1.1 Latar Belakang Projek Penyelidikan

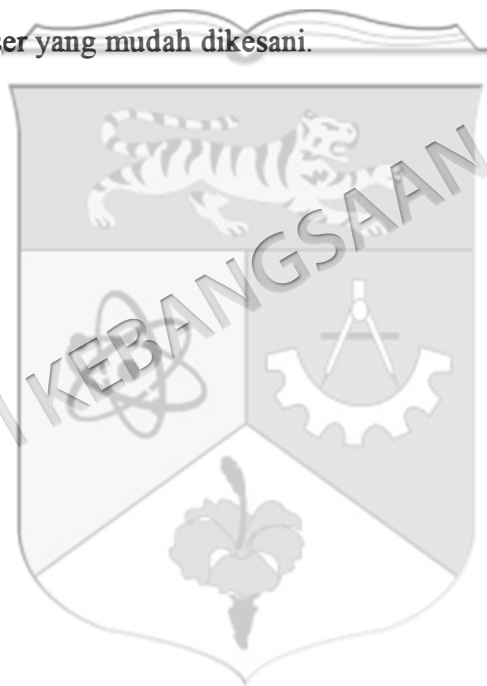
Barah merupakan penyakit yang telah diketahui lama iaitu sejak zaman tamadun purba, seperti Babylonia dan Greek (Rubin & Farber 1988). Sel-sel berproliferasi secara tidak terkawal dan terkeluar dari ciri, bentuk serta fungsi normalnya (Cappel & Anderson 1972). Sejak bertahun-tahun dahulu telah dibuktikan bahawa karsinogenesis merupakan proses beberapa langkah iaitu inisiasi, promosi, progresi dan metastasis.

Penyakit kanser atau barah menjadi penyebab kematian kedua di kebanyakan negara-negara membangun (Knekt 1991). Di Malaysia, kanser merupakan 9.3% sebab kematian di hospital kerajaan. Dengan peratusan ini kanser menduduki tempat kelima dalam senarai penyebab utama kematian di hospital kerajaan (Kementerian Kesihatan Malaysia 1988). Oleh itu kanser adalah salah satu masalah kesihatan yang perlu diberi perhatian wajar.

Beberapa faktor telah dikaitkan dengan etiologi penyakit ini. Pengaruh alam sekitar, keturunan dan diet ke atas proses karsinogenesis telah dikaji (Ames 1983). Komponen diet yang mempengaruhi proses ini termasuklah vitamin iaitu vitamin E, vitamin C, vitamin A, beta-karoten dan mineral iaitu kuprum, zink, mangan dan selenium. Pada umumnya haiwan yang diberi makan diet yang kaya dengan lemak atau kalori yang tinggi akan mempercepatkan proses karsinogenesis. Kesan vitamin dan mineral ke atas karsinogenesis agak berbeza bergantung kepada perbezaan batas percubaan yang dilakukan. Dalam kajian ini tumpuan utama adalah kepada

kesan perlindungan tokotrienol (iaitu sejenis vitamin E yang diekstrak daripada minyak kelapa sawit) semasa hepatokarsinogenesis. Minyak kelapa sawit merupakan pengeluaran pertanian utama (4.13 juta tan metrik) dan eksport komoditi utama (\$3944 juta) di Malaysia (Nik Hashim & Zulkifly 1989).

Banyak bukti menunjukkan kesan steroid berbeza ke atas proses karsinogenesis. Dalam kajian ini juga akan dipelajari kesan beberapa steroid serta kesan pemberian tokotrienol bersama-sama steroid pada proses hepatokarsinogenesis. Kajian ini menghadkan skopnya kepada enzim-enzim detoksifikasi pada hepar sebagai organ sasaran hepatokarsinogen dan plasma sebagai penanda kanser yang mudah dikesani.



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