ELLAGIC ACID

The true anticarcinogenic phytonutrient

I. Introduction

Ellagic acid is a polyphenol, found in certain fruits and nuts including grapes, strawberries, raspberries, pomegranate, Morinda citrifolia, Terminalia chebula and wallnut[1, 2]. This phenol is one of the most promising chemopreventive agents[3].

Medical findings in Europe show that Ellagic acid may reduce the incidence of birth defects[4], promote wound healing[5], reduce and reverse chemically induced liver fibrosis[6] and may help in the fight against heart disease. It also has antibacterial and antiviral properties[7].

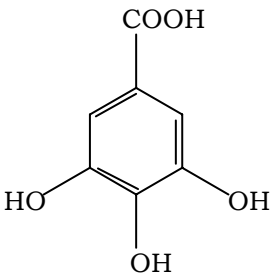
Ellagic acid acts as scavenger to "bind" with cancer causing chemicals, making them inactive[8]. It is non-toxic lung tumorigenesis chemopreventive agent[9]. Its higher dose significantly inhibits lung tumorigenesis[9].

Research in US indicates that in the laboratory Ellagic acid slows the growth of abnormal colon cells in humans[10]. It promotes apoptotic growth (natural death) of cancer cells[11].

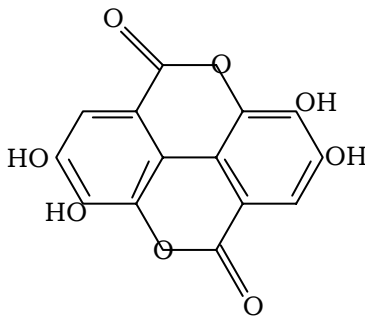
Ellagic acid inhibits chemically induced cancer in the lung, liver, skin and esophagus of rodents and TPA-produced tumor promotion in mouse skin[12].

II. Chemistry:

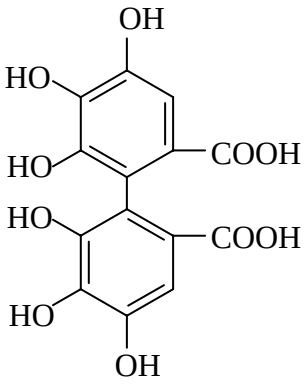
Gallotannins and ellagitannins are polyesters of glucose which on hydrolysis release the sugar and either gallic acid, Hexahydroxydiphenic acid (HHDP) or both. This HHDP rapidly lactonizes to Ellagic acid. The structures of some of these compounds are shown in Figure 1.



Gallic Acid



Ellagic Acid



HHDP

Figure 1: Chemical structures

III. Pharmacological actions:

Ellagic acid has substantial potential for decreasing the risk of tumorigenicity[13,14]. It is an antioxidant as effective as or better than αTocopherol or tertiary butylhydroxyanisole (TBA) and it shows inhibitory activity against lipid peroxidation[13]. It is a chemo-preventive agent. Ellagic acid has potential to inhibit the carcinogenic effects of at least three classes of chemical carcinogens viz. The Poly Aromatic Hydrocarbon (PAH), N-nitroso compounds and fungal toxins[15]. The ability to bind to DNA and scavenge the ultimate forms of the carcinogens to play a role in the mechanism by which it inhibits mutagenesis and carcinogenesis[16, 17].

It is a potent inhibitor of catalytic activities of two human DNA topoisomerase I & II. Hydroxyl group and the lactone groups are the most essential elements for topoisomerase inhibitory action[18].

Ellagic acid controls hemorrhage in animals and humans[19], presumably by activating Hageman factor *in vitro and in vivo* and thereby causing a state of hyper coagulability[19, 20]

It is also effective for the treatment of ulcer and gastrointestinal disorder such as constipation, heartburn, non-ulcer dyspepsia, and esophagitis[21].

IV. Preclinical studies

a. Inhibition of Skin cancer / cutaneous cancer:

Topical application of Ellagic acid had exerted strong protective effects against 3 – methycholanthrene induced skin carcinogenesis in BALB/C mice[22]. It protected NMRI Swiss mice against 7, 12-dimethyl benzo -(a)-anthracene induced skin tumours[23].

Studies[22] indicate that Ellagic acid had a profound inhibitory effect on enzyme activity, intracellular and extracellular metabolism of Benzo (a) pyrene (BP) and water soluble conjugation as well as enzyme mediated binding of hydrocarbon to keratinocyte DNA in a dose dependant manner. Hence Ellagic acid is useful in modulating the risk of cutaneous cancer resulting from exposure to these environmental chemicals.

Ellagic acid had been shown to inhibit the tumorigenicity of BP P-7, 8-diol-9, 10-epoxide 2 in newborn mice and on mouse skin[24].

b. Esophageal Cancer

Ellagic acid had produced a 50% reduction in esophageal tumors induced by N-nitroso benzlmethylamine NBMA (carcinogen) *in vivo*[25]. Barch & Fox[26] showed that it inhibited the metabolism of NBMA and the

binding of NBMA metabolites of DNA in cultured rat esophagus. It was also showed that feeding with Ellagic supplemental diet for 3 weeks resulted in a significant protection against NBMA methylation of O^6 – guanine in rat esophageal DNA[27]. Ellagic acid exhibited inhibitory effects toward preneoplastic lesions as well as neoplastic lesions induced by N-nitroso benzylmethylamine.

Study[28] indicated that Ellagic acid had the potential to act as naturally occurring inhibitor of Aflatoxin B_1 related respiratory damage.

c. Lung Tumorigenesis

Laesca[23] Showed that Ellagic acid inhibited Benzo Pyrene – induced lung tumor formation in strain A/J mice. Studies[29] suggested that Ellagic acid inhibited Benzo (a) Pyrene induced mouse lung tumorigenesis by both the inhibition of Benzo (a) Pyrene–trans–7–8–diol metabolism and of the subsequent binding of benzo Pyrene metabolites to DNA. Large doses of Ellagic acid prevented lung tumorigenesis induced by tobacco carcinogen, 4(methyl – nitrosamino) – 1 – (3 – Pyridyl) – 1 butanone (NNK) in A/J mice[30].

d. Apoptosis (natural death) of cancer cells:

The effects of Ellagic acid on cell cycle events and apoptosis had been studied in cervical carcinoma (caski) cells. Ellagic acid at a concentration of 10^{-5} M induced G arrest within 48 hrs. and Inhibited all over cell growth and induce apoptosis in Caski cells after 72 hrs of treatment. Activation of the Cdk inhibitory protein P21 by Ellagic acid suggested a role for Ellagic acid in cell cycle regulation of cancer cells[11].

e. Increase in antioxidant enzyme activity:

Ellagic acid enhanced anti-oxidant (glutathione peroxidase, quinone reductose[31] and phase II glutathione transferase) enzyme activities[32].

f. Liver fibrosis

Oral administration of Ellagic acid significantly reduced the elevated levels of enzymes, lipid peroxide and liver hydroxy proline in Carbon tetrachloride (hepatotoxic) treated animals and rectified liver pathology. Hence, Ellagic acid can act as protective agent against Carbon tetrachloride induced toxicity and subsequent inhibition of fibrosis[6].

g. Birth defects

Ellagic acid modulates 2, 3, 7, 8 – tetrachlorodibenzo – p – dioxin (TCDD) induced fetotoxicity and oxidative stress in embryonic and placental tissues of C_{57}BL/6J mice. (3–6 mg/kg per day). Ellagic acid, was administered to the pregnant mice on days 10, 11, 12 and 13 of gestation. It significantly decreased TCDD – induced malformations including cleft palate and hydronephrosis. Treatment resulted in decrease of 47 – 98%, 79 – 93% and 37 – 53% in the production of superoxide anion and lipid peroxidation in embryonic and placental tissues. Ellagic acid provides protection against TCDD – induced fetal growth retardation and increase in lipid peroxidation in embryonic and placental tissues[4].

h. Cardiac ATP ase activity:

It increases ATP ase activity in Cardiac sarcoplasmic reticulum vesicles and help in cardiac contractile responses[7].

V. Oral Dose

Ellagic acid appeared to be well tolerated by both experimental animals and humans. Rats fed with Ellagic acid (doses as high as 50 mg/kg per day upto 45 days) did not exhibit any signs of systemic toxicity[33]. Intravenously administered doses of 0.2 mg/kg Ellagic acid showed to be well tolerated by humans[34].

Antioxidants, Curcumin (400μ moles), Ellagic acid (200μ moles) & bixin (200μ moles) per kg body weight provided protection against chromosome damage produced by radiation in mice[35].

Castonguay et. al 1994, studied the inhibition of lung tumorigensis at four dose levels of Ellagic acid. Mice fed with 4 g of Ellagic acid/kg diet reduced by 54% the lung tumor multiplicity[9].

VI. Nutraceutical Applications

Ellagic acid is an anti-oxidant[31, 32], hepatoprotectant[6], anti-carcinogen[3] and antimutagenic[38]. It is a naturally occurring inhibitor of carcinogenesis in foodstuffs[2]. Ellagic acid can be used to treat gastrointestinal disorders[21].

VII. Topical Applications of Ellagic acid

1. Inhibitory effect of Ellagic acid on melanogenesis.

Ellagic acid, a naturally existing small molecular polyphenol, has high affinity for Cu at the active site of tyrosinase. It has inhibitory effect on melanogenesis under UV – induced skin pigmentation in both brownish guinea pig and human. The utility of Ellagic acid in a six week double – blind clinical trial was rated slightly useful or better in 86% of subjects. No adverse reaction was observed through the trial period. These results suggested that Ellagic acid is a useful agent for treating pigmentations such as spots and freckles produced by UV[36].

Ellagic acid applied to the skin of guinea pig *in vivo* had a higher skin whitening effect than the pure Quercetin, Catechin and Kojic acid[37]

2. Collagen Synthesis (wound healing)

Addition of 0.5 μg/ml Ellagic acid to the cultured Keratinocytes increased the collagen type VII synthesis by 64%. Its application reinforces the dermal epidermal junction or improving hair condition by increasing the proportion of collagen VII in the presence of Keratinocytes and or fibroblasts. Ellagic acid tones up the skin, reduces wrinkles and effects hair conditioning[5].

3. Ellagic acid is a potential chemopreventive agent against skin cancer.

VIII. Recommended level for topical application

For skin preparations, such as sunscreen, skin whitening, wound healing and anti-inflammatory creams 0.3 to 1% by weight can be used[37].

Ellagic acid alkali metal salts, sodium salt or magnesium salt can be used as UV absorbents. 0.2% of sodium ellagate and 0.5% of magnesium salt are the permissible limits[37].

References

1. Bate – Smith, E.C. In the pharmacology of plant phenolics Fair bairn, J.W. et. al, Ed. Academic press: New York (1959); pg. 133 – 147;

2. Santappa M and Sundara Rao V.S., (1982) – Journal of Scientific and Industrial Research Vol. 41, 1982 Pg. 705 – 718;

3. Kelloff, G.J, Malone, W.F., Boone, C.W., Sigman, C.C., Fay, J.R. Semin Oncol. 1990, 17, 438 – 455;

4. Hassoun, E.A., Walter A.C., Al Sharif, N.Z., Stolis, S.J., (1997) Toxicology, 124 (1), 27 – 37;

5. PCT Int. Appl. WO 99, 16, 415, 1999.

6. Thresiamma, K.C and Kuttan R (1996); Indian J Physiol Pharmacol 40(4): 363 – 366;

7. Antipenko A.Y., Spielman A.I, Kirchberger M.A., J. Pharmacol. Exp. Ther 1999, 290 (1) 227-234.

8. Castonguay A. Boukharta M., Teel R (1998)- Chem. Res. Toxicol. 11(11), 1258 – 1264;

9. Castonguay A, Boukharta m, Jalbert G (1994); Food Phytochemicals for cancer prevention I, American Chemical Society; Washington DC 294-302.

10. Narayanan BA, Re GG (2001) Anti cancer Res. Jan-Feb, 21(1A): 359 – 364;

11. Narayanan B.A., Geoffroy O., Willingham MC., Re.GG, Nixon DW. (1999) cancer Lett Mar 1, 136(2): 215 – 221;

12. Stoner GD, Mukhtar H., 1995 – J. Cell Biochem Suppl. 22 : 169 – 180;

13. Zee – Cheng, R.K.Y. and Chang, C.C.J (1986) – Drugs of the Future 11, 1029 – 1033;

14. Hayatsu, H, Arimoto, S. And Negishi, T., (1988) – Dietary inhibitors of mutagenesis and carcinogenesis Mut. Res., 202, 429 – 446;

15. Mandal S., Ahuja A, Shivapurkar N.M., Cheng S.J, Groupman J.D and Stoner G.D., (1987) Carcinogenesis 8, 11, 1651 – 1656.

16. Teel, R.W., Stoner, G.D, Babcock, M.S. Dixit, R& Kim, K (1986), Cancer detect Prev. 9, 59 – 66;

17. Wood, A.W., Huang, M.T., Chang, R.L., New mark, H.L., Lehr, R.E., Yagi, H, Sayer, J.M., Jerina, D.M. and Conney. A.H. (1982).Proc. Natl. Acad, Sci USA, 79, 5513 – 5517.

18. Constantinou A., Stoner G.D., Mehta R., Rao K, Runyan C., Moon R. (1995) (Nurt. Cancer, 23(2): 121 – 130.

19. Cliffton, E.E. (1967). Am. J. Med. Sci 254, 483 – 490;

20. Botti, R.E, and Ratnoff, O.D. (1964) – J. Lab. Clin. Med., 64, 385 – 398.

21. Rajagopalan, Tuticorn G. Khambe, Ashok D. Us.US. 5, 843, 987, 1998;

22. Mukhtar, H., Benjami J. Del Tito, Jr. Marcelo L, Das M and Bickers R.D, (1984) Carcinogenesis 5, 12, 1565 – 1571;

23. Lesca, (1983). Carcinogenesis 4 : 1651 – 1653;

24. Chang, R.L. Huang, M.T., Wood, A.W., Wang, C.Q; New Mark, H.L., Yagi H, Sayer, J.M., Jerina, D.M, and Canney, A.H., (1985) Carcinogenesis 6 : 1127 – 1133;

25. Mandal S., Shivapurkar N.M., Galati A.J., Stoner G.D (1988) Carcinogenesis 9, 1313 – 1316;

26. Barch., D.H. & Fox (1988) Cancer Res., 48, 7088 – 7092;

27. Mandal S., Sotner G.D. – (1990) Carcinogenesis, 11, 1 55 – 61;

28. Mandal S. Ahuja A, Shivapurkar, N.M., Chang S.J., Groupman J.D., Stoner G.D (1987) Carcinogenesis 8, 11, 1651 – 1656;

29. Dixit, R., Teel W.r, Daniel B.D., Stoner G.D. (1985), 45, 2951 – 2956;

30. Castonguay A, Boukharta, M., Teel, R (1998), Chem. Res. Toxicol. 11, 11, 1258 – 1264;

31. Barch DH, Rundhaugen LM 1994 – Carcinogenesis Sep, 15(9) 2065 – 2068;

32. Barch DH Rundhaugen LM, Stoner, G.D., Pillay, N.S., Rosche W.A Carcinogenesis 1996, 17(2); 265 – 269;

33. Doyle B. and Griffits C.A (1980) – Xenobiotica 10, 247 – 256;

34. Orelami A and Cliffton, E.E., (1967) – Thrombi. Diath Haemorh 17, 165 – 175;

35. K.C. Thresiamma J. George & R. Kuttan, (1995); J. Exep. Clin. Research 14(4) 427 – 430;

36. Tanak. Y (1997), fragrance J., 25(9) 37 – 42;

37. Patents:

    i. JP 02, 273, 613, 90, 273, 613, 1990
    ii. DE 19, 730, 408, 1998;
    iii. JP 02, 237, 90 b (90, 237, 906) 1990
    iv. JP 02, 231, 408 (90, 231, 408) 1990
    v. JP 02, 258, 707 (90, 259, 707) 1990
    vi. JP 02, 231, 407 (90, 231, 407) 1990
    vii. JP 02, 269, 176 (90, 269, 176) 1990

viii. Eur Pat. 294, 808 (C1 A61 K7/48) 1988

38. Gorski T, Gorecka D, Sikora M. 1997 Pol. J. Envi Stud. 6(1) 29-32.

****