WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 5, 1618-1624. Review Article ISSN 2277– 7105

ROLE OF NARINGENIN AND ITS DERIVATIVES IN ANTIMUTAGENICITY - A REVIEW

K. Chandan*[1], R. Keerthiga[1] and J. Vinoth Arulraj[2]

[1]Final Year, Anna Bio Research Foundation, Department of Biotechnology, Arunai Engineering College, Tiruvannamalai, Tamilnadu – 606603, India.

[2]Assistant Professor, Anna Bio Research Foundation, Department of Biotechnology, Arunai Engineering College, Tiruvannamalai, Tamilnadu – 606603, India.

Article Received on
23 March 2016,
Revised on 12 April 2016,
Accepted on 02 May 2016
DOI: 10.20959/wjpr20165-6219

***Corresponding Author**
K. Chandan
Final Year, Anna Bio Research Foundation, Department of Biotechnology, Arunai Engineering College, Tiruvannamalai, Tamilnadu – 606603, India.

ABSTRACT

Mutagenicity, was one of the main reason for the development of various diseases including cancer and diabetes. The mutagenic effects were decreased by use of natural antimutagenic agents which is most commonly present in edible plants. Among them naringenin, a natural flavanone exhibits antimutagenicity against gastric cancer cell line, steroids, chemotherapeutic drugs and genotoxic compounds. Present review attempts to furnish an outline of naringenin and its role in antimutagenicity.

KEYWORDS: Mutagenicity, Naringenin, Antimutagenicity.

INTRODUCTION

The capacity of the compound which affects the DNA structure and topoisomerase responsible for the genomic fidelity is known as genotoxicity.[9, 19] Combination of cytostatic drugs which were mostly genotoxic was used in treating patients who were suffering from disseminated malignant diseases. As the result, chemotherapy drugs not only affect tumor cell but also normal tissues and it undergoes cellular and DNA damage.[30] Phytochemicals, which are bioactive plant compounds present in fruits, vegetables, grains and other plant foods reduces the risk of major chronic diseases.[26] Antimutagen and antioxidative agents have been identified as anticarcinogens.[3] Thus, the genotoxic effects of mutagenic and carcinogenic factors can be reduced by regular intake of plants possessing antimutagenic and antioxidative agents.[14] Flavanoids, an extract of plants and fruits have been widely used in cancer therapy and it also

possesses multiple biological activities.[8, 34] Naringenin, a citrus fruit flavonoid possesses both antimutagenic and anticarcinogenic activities.[10, 17] Recent studies have shown that naringenin inhibits cancer cells including epidermoid carcinoma, human hepatocellular carcinoma, bladder cancer and breast cancer.[1, 2, 10, 12, 17]

NARINGENIN- A NATURAL FLAVANONE

Naringenin [2, 3 dihydro-5, 7 dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran 4-one], a natural flavanone was derived from hydrolysis of naringin and it is one of the most important water insoluble antioxidants. Naringin (Naringenin- 7 rhamnoglucoside), a bitter constituent were mostly found in grape juices, flowering parts, peels as well as vegetative parts.[20] Naringenin was insoluble in water where as naringin solubilise in water.[23] Different natural food sources including propolis, citurus species and skin of tomatoes contains naringenin and its glycosylated form naringin.[6, 33] Naringenin possesses electron donating activity and it quenches free radicals by its 4'hydroxyl group present in B-ring.[5, 24] Free radical scavenging and antioxidants activity plays an important role in preventing cardiovascular diseases.[16]

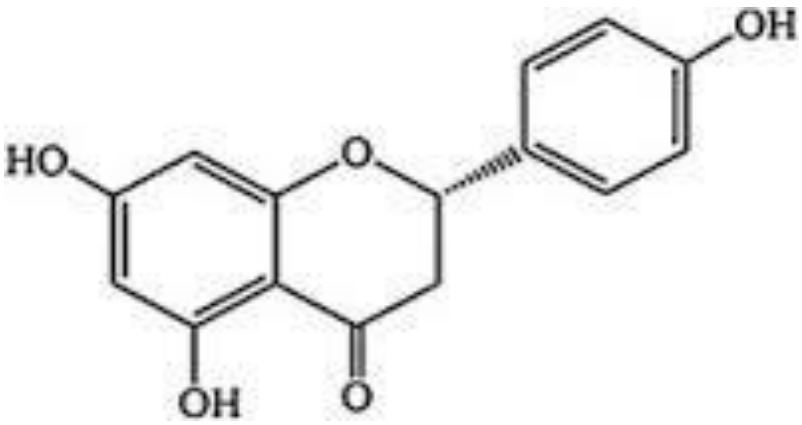

Fig.1 Chemical Structure of Naringenin[29]

PROPERTIES OF NARINGENIN

Naringenin and their derivatives possess both strong antioxidants potentials and plenty of protective effects required for the improvement of human health. Osteoporosis, cardiovascular and cancer were treated by naringein and helps in lipid lowering. It also shares insulin like properties. Naringenin possesses impressive pharmacological profile which would useful in treatment of different diseases.[29]

PHARMACOKINETICS OF NARINGENIN

Oral administration of naringenin was detected in the plasma but it is reported to be below accurate detection limits[13, 15] and it has not exceeded above 4mM.[15] It is possible for

naringenin to get accumulated within tissue (liver, tissues and membranes) and reach higher concentration than observed in the plasma due to its lipophilic nature.

COMBINED ANTICANCER EFFECTS OF NARINGENIN AND ABT-737 ON GASTRIC CANCER CELLS

Colony formation and gastric cancer cell growth were inhibited when naringenin used in combination with ABT-737. In addition it induces apoptosis through activation of caspase-3. Through down regulation of Akt and caspase 3-activation naringenin induces apoptosis in acute myeloid leukemia cells.[21] Similarly, it inhibits bladder cancer cell migration through the down regulation of matrix metalloproteinase-2 pathway and Akt respectively.[17]

GENISTEIN AND GINGEROL REDUCES GENOTOXICITY INDUCED BY NORETHANDROLONE AND OXANDROLONE

Genistein is synthesized from naringenin which was catalysed by isoflavone synthase (cytochrome P 450 enzyme) through a ring migration reaction. The number of abnormal cell with chromosomal aberration induced by oxandrolone and norethandrolone were equally reduced by both geinstein and gingerol. 30µM and 40µM of genistein, 20µM and 30µM of gingerol were effective in reducing the genotoxicity of 30 µM and 40 µM of orethandrolone and norethandrolone. Here, dose dependent decrease in number of abnormal metaphases were observed.[32]

GENISTEIN SUPPRESSES DOXORUBICIN ASSOCIATED GENOTOXICITY

Growth inhibitory effects of most chemotherapeutic agents on selected cancer was enhanced when antioxidants were used in combination with chemotherapeutic drugs.[4, 22, 25] Possibility for development of secondary tumors and genotoxic damage by doxorubicin was reduced in treatment with antioxidant genistein.[31]

TREATMENT FOR LOMEFLOXACIN INDUCED GENOMIC INSTABILITY IN MICE BY NARINGENIN

Micronuclei formation in bone marrow and chromosomal aberration in mice due to lomefloxacin were reduced by pretreatment of mice with naringenin. The protective effect of naringenin increases in dose depended manner. Here, the exact mechanism of action for naringenin on lomefloxacin was not clearly understood. However, one possible explanation is that, before free radicals reaches DNA naringin would undergo interception of free radicals.[28] Lipid peroxidation and GSH (oxidative markers) were measured after the animals

are treated with lomefloxacin in order to evaluate wheather the antimutagenic effect observed were due to enhancement of free radicals generated by lomefloxacin. The result shows that lomefloxacin induce lipid peroxidation and prevents GSH reduction which were due to pretreatment of naringenin. Increased GSH level demonstrates that modulation of cellular antioxidant levels may be involved in protection by naringenin.[27]

INFLUENCE OF NARINGIN ON CADMIUM INDUCED GENOMIC DAMAGE

Cadmium is highly toxic due to oxidative detoriaration of biomolecules including proteins, lipids and DNA.[11] It was observed at 20µM and 40µM of cadmium increases the total chromosomal aberration in human lymphocytes[7] which were reduced in further treatment with naringin. One possible explanation for the mechanism carried out is that, before free radicals reaches DNA naringin would undergo interception of free radicals.[28] High dose of cadmium involves in induction of sister chromatid exchange. Even treatment with naringin not exert any protection against sister chromatid exchange induced by cadmium.

NARINGIN TREATMENT FOR CHROMOSOMAL INSTABILITY IN DIABETIC RATS

Natural antioxidants prevent oxidative stress related sequences, amoung them certain antioxidants possess genotoxic or carcinogenic potentials.[3, 18] However, treatment with naringin was devoid of genotoxicity and cytotoxicity in both diabetic and non-diabetic rats. It also protects in increase of stomatic and germinal chromosomal instability in diabetes induced rats. After four weeks of Streptozotocin administration the diabetic rats were euthanized. When compared to the control rats it were observed that the frequencies of chromosomal instability and oxidative stress markers were significantly higher in diabetic rats. The mechanism by which naringin inhibits diabetes induced chromosomal instability was not clearly understood. However, one possible explanation is that, before free radicals (generated by diabetes) reaches DNA naringin would undergo interception of free radicals.[28]

CONCLUSION

Mutation is one of the main reason for the development of various diseases including cancer. In this review, it is shown that naringenin and its derivatives were less genotoxic and used as an anti cancer and anti diabetic agent. Further, it is used in treatment for cell damage (normal cells) caused by chemotherapeutic drugs which was a major side effect of chemotherapy. The mechanism by which naringin inhibits genotoxicity was not clearly understood. However, one possible explanation is that, before free radicals reaches DNA naringenin would undergo

interception of free radicals. Thus, further studies have to be carried out in order to find exact mechanism of action of naringenin.

REFERENCES

1. Ahamad MS, Siddiqui S, Jafri A, Ahmad S, Afzal M and Arshad M: Induction of apoptosis and antiproliferative activity of naringenin in human epidermoid carcinoma cell through ROS generation and cell cycle arrest. PloS one, 2014.
2. Arul D and Subramanian P: Naringenin (citrus flavonone) induces growth inhibition, cell cycle arrest and apoptosis in human hepatocellular carcinoma cells. Pathol Oncol, 2013; Res 19: 763-770.
3. B.N.Ames. Dietary carcinogens and anticarcinogens, oxygen radicals and degenerative diseases. Science, 1983; 221(4617): 1256–1264.
4. Blaylock RL. A review of conventional cancer prevention and treatment and the adjunctive use of nutriceutical supplements and antioxidants: Is there a danger or a significant benefit. J Am Nutr Assoc., 2000; 3: 75–95.
5. Cao G, Sofic E, Prior RL. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. Free Radic Biol Med. 1997; 22(5):749-60.
6. Chang CC, Yang MH, Wen HM, Chern JC. Estimation of total flavonoid content in propolis by two complimentary colorimetric methods. J Food Drug Anal. 2002; 10:178–182.
7. Dilek Yılmaz, Nilufer Cinkilic Aydemir, Ozgur Vatan, Ece Tuzun and Rahmi Bilaloglu. Influence of naringin on cadmium-induced genomic damage in human lymphocytes in vitro. Toxicology and Industrial Health, 2011; 1–8.
8. Donato F. Romagnolo and John A. Milne. Nutrition Proteomics and Cancer Prevention Opportunities and Challenges for Nutritional Proteomics in Cancer Prevention. The Journal of Nutrition Supplement, 2012
9. Eastmond DA, Hartwig A, Anderson D, Anwar WA, Cimino MC, Dobrev I, Douglas GR, Nohmi T, Phillips DH, Vickers C. Mutagenicity testing for chemical risk assessment. Mutagenesis. 2009; 24: 341–349.
10. Ekambaram, G., P. Rajendran, R. Devaraja, R. Muthuvel and D. Sakthisekaran. Impact of naringenin on glycoprotein levels in N-methyl-N-nitro-N-nitrosoguanidine induced experimental gastric carcinogenesis Anticancer Drugs, 2008; 19: 885-890.
11. Fotakis G, Cemeli E, Anderson D, and Timbrell JA. Cadmium chloride-induced DNA and lysosomal damage in a hepatoma cell line. Toxicology In Vitro, 2005; 19: 481–489.

12. Hatkevich T, Ramos J, Santos−Sanchez I and Patel YM: A naringenin-tamoxifen combination impairs cell proliferation and survival of MCF-7 breast cancer cells. Exp Cell Res. 2014; 327: 331-339.
13. Hertog MG, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, Giampaoli S, Jansen A, Menotti A, Nedeljkovic S, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study, Arch Intern Med. 1995; 27; 155(4): 381-6.
14. Ikken Y, Morales P, Martinez A, Marin ML, Haza AI, Cambero MI. Antimutagenig effects of fruit and vegetables. J. Agric. Food Chem., 1999; 47: 3257-3264.
15. Ishii K., et al. Determination of naringin and naringenin in human urine by high performance liquid chromatography utilizing solid-phase extraction. J Chromatogr B Biomed Appl, 1997; 704: 299–305.
16. Joe A. Vinson, Xiquan Liang, John Proch, Barbara A. Hontz, John Dancel, Nicole Sandone. Polyphenol Antioxidants in Citrus Juices: in vitro and in vivo Studies Relevant to Heart Disease. Advances in Experimental Medicine and Biology, 2002; 113-122.
17. Liao B et al. Using multi-instance hierarchical clustering learning system to predict yeast gene function. PLoS One, 2014.
18. M. Lopez-Lazaro. Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Molecular Nutrition and Food Research, 2008; 52(1): S103–S127.
19. Maurici, D., Aardema, M., Corvi, R. et al. Carcinogenicity. Altern Lab Anim., 2005; 33(1): 177-82.
20. Pablo S. Jourdan, Cecilia A. McIntosh and Richard L. Mansell. Naringin Levels In Citrus Tissues. Plant Physiol., 1985; 77: 903-908.
21. Park JH, Jin CY, Lee BK, Kim GY, Choi YH and Jeong YK. Naringenin induces apoptosis through downregulation of Akt and caspase-3 activation in human leukemia THP-1 cells. Food Chem Toxicol., 2008; 46: 3684-3690.
22. Prasad, K.N. Modulation of the effects of tumor therapeutic agents by vitamin C, Life Sci., 1980; 27: 275-80.
23. Pulley G. N. Solubility of naringin in water. Ind. Eng. Chem. Anal., 1936; Ed. 8: 360-360.
24. Rice-Evans C. Flavonoid antioxidants. Curr Med Chem., 2001; 8(7): 797-807.

25. Ripoli, E.A.P., B.N. Rawa & M.M. Webber. J. Urol., 1986; 136: 529-31.
26. Rui Hai Liu. Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action. The journal of Nutrient, 2004.
27. Sabry M. Attia. Abatement by naringin of lomefloxacin-induced genomic instability in mice. Mutagenesis, 2008; 23(6): 515–521.
28. Saleh A. Bakheet and Sabry M. Attia. Evaluation of Chromosomal In stability in Diabetic Rats Treated with Naringin. Oxidative Medicine and Cellular Longevity, 2011; 9 pages.
29. Sumathi R, Tamizharasi S and Sivakumar T. Bio-Dynamic Activity of Naringenin–A Review. International Journal of Current Advanced Research, 2015; 4(8): 234-236.
30. T.J. Elsendoorn, N.I. Weijla, S. Mithoea, A.H. Zwindermanb, F. Van Damc, F.A. De Zwartc, A.D. Tatesc, S. Osantoa . Chemotherapy-induced chromosomal damage in peripheral blood lymphocytes of cancer patients supplemented with antioxidants or placebo. Mutation Research, 2001
31. Tanveer Beg, Yasir H. Siddique, Gulshan Ara, Asfar S. Azmi and Mohammad Afzal. Genistein Suppresses Doxorubicin Associated Genotoxicity in Human Lymphocytes. Latin American Journal of Pharmacy (formerlyActa Farmacéutica Bonaerense) Lat. Am. J. Pharm., 2011; 30(7): 1317-24.
32. Tanveer Beg, Yasir Hasan Siddique, Gulshan Ara, Jyoti Gupta and Mohammed Afzal. Antigenotoxic effect of genistein and gingerol on genotoxicity induced by norethandrolone and oxandrolone in cultured human lymphocytes. International Journal of Pharmacology, 2008; 4(3): 177-183.
33. Yamamoto, Akifumi Nakayama, Yuka Yamamoto and Shiro Tabata. Val216 decides the substrate specificity of a-glucosidase in Saccharomyces cerevisiae Keizo, Eur. J. Biochem. 2004; 271: 3414–3420.
34. Yuan J, Zhang L, Kan X, Jiang L, Yang J, Guo Z, Ren Q. Origin and molecular characteristics of a novel 2013 avian influenza A(H6N1) virus causing human infection in Taiwan. Clin Infect Dis., 2013.