ejpmr, 2022, 9(12), 127-130

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ANTI-CARCINOGENIC POTENTIAL OF BIOCHANIN-A: AN OVERVIEW

***[1]Gupta Ritesh Vinod and [2]Shalini Singh**

*[1]Research Scholar, Institute of Pharmaceutical Sciences and Research, Unnao.
[2]Associate Professor, Institute of Pharmaceutical Sciences and Research, Unnao.

***Corresponding Author: Gupta Ritesh Vinod**

Research Scholar, Institute of Pharmaceutical Sciences and Research, Unnao.

Article Received on 03/10/2022 **Article Revised on 24/10/2022** **Article Accepted on 14/11/2022**

ABSTRACT

Phytoestrogens are substances that are present in plants that have an estrogen-like molecular structure and size. An isoflavone called biochanin A (also known as 5,7-dihydroxy-4'-methoxy-isoflavone, or BCA) is found in red clover, cabbage, alfalfa, and many other herbal items. It is a naturally found isoflavone found in several clover species' legumes, most notably red clover, as well as in numerous herbal nutritional supplements. Numerous research looking at the therapy of cancer have explored BCA. In 1988, a hamster embryo cell culture experiment was conducted, and it shown that BCA prevented carcinogen activation. Some kinds of cancer have been shown to occur less frequently when COX-2 is inhibited. BCA protects against oxidative stress and prevents invasive enzyme production and activity. The most significant finding was that, at the moderate concentration at which it suppressed cancer cells, BCA had no such effects on healthy tissues or cells. BCA is regarded as a powerful cancer-fighting chemo preventive and/or therapeutic agent. Overall, Biochanin-A appears to provide a dual targeted agent that inhibits two processes, invasion, and angiogenesis. The target genes' transcription is then stimulated by the translocation of the freed NF-B dimmers into the nucleus. In concluded that BCA has anti-cancer potential when studied in different cancer types. It might be recommended in the treatment of carcinoma as a part of chemotherapy.

KEYWORDS: Biochanin-A, review, COX-2, anti-carcinogenic, colon cancer.

INTRODUCTION

Phytoestrogens are substances that are present in plants that have an estrogen-like molecular structure and size. The most well-known of the several estrogenic chemicals are plant flavonoid isoflavones (Heinonen et al., 1999). Soybeans and soy products are the main dietary sources of isoflavones for people. These food kinds have several consequences when ingested (Vitale et al., 2013). According to epidemiological research, populations who consume a lot of soy have decreased incidences of a few cancers, including breast, prostate, bladder, stomach, and colon cancer.

Biochanin-A

An isoflavone called biochanin A (also known as 5,7-dihydroxy-4'-methoxy-isoflavone, or BCA) is found in red clover, cabbage, alfalfa, and many other herbal items (Cassady et al., 1988). BCA can be used as an alternative to hormone therapy and may appear as an aglycon. By binding DNA and some proteins or by functioning as a competitive substrate for some enzymes, BCA plays intricate roles in the regulation of numerous biological functions (Liang et al., 2019). Another well-researched isoflavone, BCA is the methylated precursor of the isoflavone genistein. Intestinal microorganisms in the intestine convert BCA into its demethylated form. The biological effects of BCA, however, differ from those of GEN both in vitro and in vivo. Due to its alleged biological activities, such as its antioxidant, anti-inflammatory, anti-infective, and anticarcinogenic effects, medical research on BCA has recently increased. BCA has also been used for a few purposes, including the treatment of pain and oestrogen deficiency, as well as to lessen the severity of nerve damage.

It is a naturally found isoflavone found in several clover species' legumes, most notably red clover, as well as in numerous herbal nutritional supplements. It is abundant in zigzag clover (*Trifolium medium*), but less so in red clover (*Trifolium pratense*), crimson clover (*Trifolium incarnatum*), haresfoot clover (*Trifolium arvense*), hungarian clover (*Trifolium pannonicum*), and red-feather clover (*Trifolium rubens*). Other plants that contain it include soy, alfalfa, peanuts, and chickpeas (Breikaa et al., 2013).

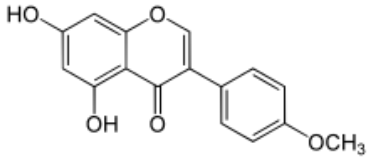

Fig. 1: Structure of Biochanin-A.

Anti-cancer potential of BCA

Numerous research looking at the therapy of cancer have explored BCA. In 1988, a hamster embryo cell culture experiment was conducted, and it shown that BCA prevented carcinogen activation. Then, investigations examining the anticancer efficacy of BCA in various cancer cell lines and animal models were conducted. Numerous tumour types, including lung cancer, osteosarcoma, breast cancer, pancreatic cancer, g.i.t. cancer, and malignancies of the central nervous system, may be suppressed by BCA (Sehm et al., 2014). The anticancer use of BCA may be broader due to its targeting of anticancer activity, notably in malignant brain tumours, while its capacity to prevent the proliferation of some types of cancer cells was weaker than that of GEN. By binding to DNA, BCA has an inhibitory effect on the metabolism of certain carcinogens, such as benzo(a)pyrene, and may be effective as a chemo-preventive agent against hydrocarbon-induced carcinogenesis. BCA is a powerful cytochrome P450 (CYP) inhibitor. According to Wang et al. (2008), BCA dramatically lowers the production of prostaglandin E2 and thromboxane B2 as well as the activity of CYP19/aromatase, which inhibits cyclooxygenase-2 (COX-2) (Lim et al., 2013). It has been demonstrated that cancer growth, particularly at regions of inflammation, relates to the chronic activation or overexpression of COX-2. Some kinds of cancer have been shown to occur less frequently when COX-2 is inhibited. BCA protects against oxidative stress and prevents invasive enzyme production and activity.

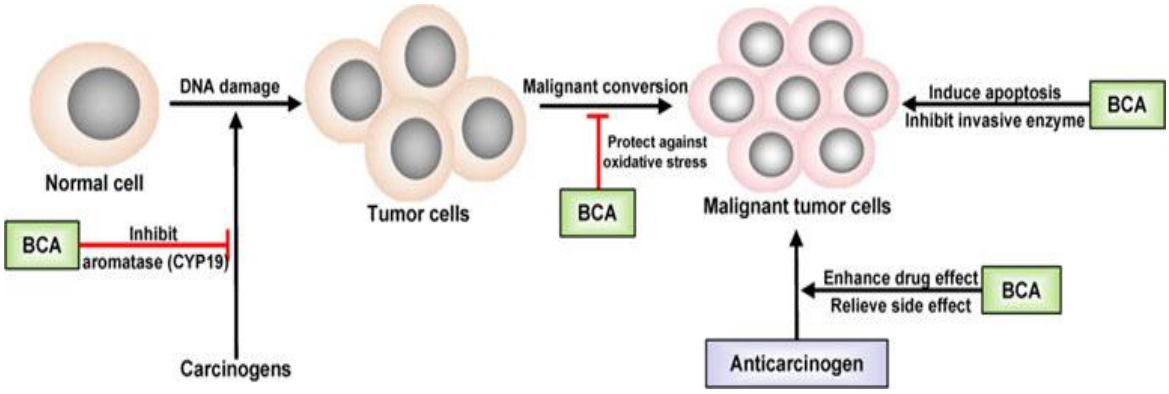

Fig. 2: Anticancer role of BCA.

By downregulating Ki-67, caspase-3 and caspase-9 are activated, causing apoptosis, while matrix metallopeptidase-2 (MMP-2) and vascular endothelial growth factor (VEGF) are downregulated, successfully inhibiting the development of lung cancer cells (Lai et al., 2018). BCA enhanced the expression of crucial proteins in the NF-B and mitogen-activated protein kinase (MAPK) signalling pathways and inhibited cell migration and invasion in a dose-dependent manner. In colon cancer cells cultured in vitro, BCA dramatically increases radiotoxicity as a notable pro-oxidant agent (Puthli et al., 2013). Fig 2. shows the anticancer effects of BCA. Additionally, BCA lessens the adverse effects of various anticarcinogens while enhancing their benefits. The most significant finding was that, at the moderate concentration at which it suppressed cancer cells, BCA had no such effects on healthy tissues or cells. BCA is regarded as a powerful cancer-fighting chemopreventive and/or therapeutic agent.

The higher expression of iNOS may increase the nitric oxide radical at the inflammation millue, and Biochanin-A not only decreases the expression of iNOS and pro-inflammatory cytokines, but also involved in nitration, thus could inhibit both inflammation and carcinogenesis, as demonstrated in our inflammation system using LPS-mediated macrophage model (Das et al., 2006). According to the MTT experiment, the Biochanin-A concentration that caused the suppression of iNOS expression in RAW 264.7 was not cytotoxic.

As evaluated by us, it does, however, have cytostatic effects at lower concentrations on a number of gastrointestinal cell lines, including colon, oesophageal, and stomach cancer lines. Through the inhibition of NF-B, biochanin-A therapy greatly reduces the LPS-stimulated NO generation and iNOS expression at the physiological concentration and negatively controls the inflammatory pathway in macrophages. The physiological activation of iNOS is linked to inflammation since the expression of inflammatory molecules like IL-1, TNF, and IL-6 is ten times higher in stimulated cells than in unstimulated cells. LPS-induced pro-inflammatory cytokines like TNF- are regulated by the p38 MAPK. macrophage synthesis of IL-1 and IL-6. The synthesis of proinflammatory molecules is caused by the phosphorylation of MAPK, which is a component of LPS-mediated inflammation. Phosphop-38 MAPK enters the nucleus and phosphorylates the ATF-2 transcription factor. Tyrosin phosphorylation and p38 MAPK phosphorylation are both inhibited by genistein, an isoflavonoid similar to Biochanin-A. This suggests that the Biochanin-A may suppress the MAPK p38 activation-related tyrosine phosphorylation signalling at this point. The in vitro kinase experiment might be better demonstrated utilising pure PKC/Raf/MEK/p38 as a

source of substrate, but we are proposing here the disruption of p38 activity by Biochanin-A.

Da Silva et al. (1997) and Chen and Wang (1999) both reported on the involvement of iNOS induction through NF-B activation, but this is the first evidence that Biochanin-A is engaged in the disturbance of this pathway leading to anti-inflammatory activity.

In breast cancer, it selectively targets HER-2+ SK-BR-3 breast cancer cells and inhibits multiple deregulated mechanisms associated with malignant transformation. Biochanin-A drastically reduced cell invasion, inhibited multiple signalling pathways and lowered the cell viability in a dose dependent manner (Sehdev et al., 2009).

In brain tumour, malignant gliomas like glioblastoma multiforme are the most lethal form of adult brain tumor (Jain et al 2015) has demonstrated that Biochanin-A inhibits invasion in human glioblastoma cells. Biochanin-A inhibited endothelial cell functions observed in gliomas such as migration, invasion, and cell viability. The activation of several proangiogenic proteins such as ERK, AKT, and mTOR was significantly inhibited. Overall, Biochanin-A appears to provide a dual targeted agent that inhibits two processes, invasion, and angiogenesis.

In Pancreatic cancer, the extraordinary aggressiveness of pancreatic cancer cells is thought to be caused by mutations in both tumor-promoting and tumor-suppressor genes. Because their greater amounts of EGFR and EGF mRNA relative to normal pancreas cells encourage cellular proliferation in an autocrine way, pancreatic cancer patients have a poorer postoperative survival time found that Biochanin-A dramatically reduced pancreatic cancer cell survival (MTT and annexin V staining), proliferation (colony formation and mitogenic signalling), and progression (inhibition of migration and invasion). It has been shown mechanistically that Biochanin-A inhibited the activation of the AKT and MAPK pathways in pancreatic cancer cells (Szliszka et al. 2013).

In Colon cancer, Gamma radiation was shown to limit the radioresistant HT29 colon cancer cell line's ability to develop when Biochanin-A was present. Biochanin-A increased lipid peroxidation, promoted an increase in the formation of reactive oxygen species, and enhanced the potential of the mitochondrial membrane when paired with radiation. Additionally, Biochanin-A increased the activity of caspase3 and induced apoptosis in the radio resistant HT29 colon cancer cells, which increased the risk of DNA damage. Sulfotransferases, a group of phase II drug metabolising enzymes, are essential for the detoxification of xenobiotics and the regulation of biological signalling molecule activities. Sulfotransferases' poor regulation of biological signalling molecules can lead to cancer or other diseases (Chen et al., 2010).

NF-B heterodimer, which is mostly made up of the two proteins p50 and p65, is stationed at the cytosol at rest by interacting with I-B inhibitory proteins (Baeuerle and Henkel, 1994). The I-B is stimulated by LPS and undergoes phosphorylation, ubiquitination, and dissociation into monomers of p65, p50, c-Rel, etc. The target genes' transcription is then stimulated by the translocation of the freed NF-B dimmers into the nucleus. Some studies suggest that Biochanin-A decreases iNOS expression via translocating and inhibiting the gene's transcription, which is corroborated by the p65 translocation and cis-activation luciferase data. It was clear from our kinase test, which used GST-IB as the substrate, that IKK-1 and IKK-2 phosphorylation was suppressed in a dose-dependent manner, suggesting that Biochanin-A was suppressing the signalling pathway that was responsible for the LPS-mediated inflammation. We cannot not rule out the possibility that Biochanin-A directly inhibits IKK-1 and IKK-2 phosphorylation. Purified protein could be used in the in vitro phosphorylation experiment as the substrate to overcome this problem. Finding out how Biochanin-A prevents LPS-induced NF-B activation and phosphorylation of p38 MAPK is an intriguing question. LPS activates TLR to produce a signal, attracting MYD 88 and TRAF6 (TNF receptor associated factor 6). NF-B inducing kinase and p38 MAPK are recruited by TRAF6 to the IKK complex, which then activates it.

CONCLUSION

In rat liver and intestines, Biochanin-A can greatly increase sulfotransferases enzyme activity and gene expression. These findings may also provide light on Biochanin-A's anticancer properties. In addition, we have found that NF-B binding activity is inhibited at various concentrations of Biochanin-A, and this suppression of binding is consistent with LPS-induced NO generation.

In concluded that BCA has anti-cancer potential when studied in different cancer types. It might be recommended in the treatment of carcinoma as a part of chemotherapy.

SOURCE OF FUNDING

Nil.

CONFLICT OF INTEREST

None.

REFERENCES

1. Baeuerle, P.A., Henkel, T., Function and activation of NF-kappa B in the immune system. Annu. Rev. Immunol, 1994; 12: 141–179.
2. Breikaa RM, Algandaby MM, El-Demerdash E, Abdel-Naim AB. Multimechanistic antifibrotic effect of Biochanin-A in rats: implications of

proinflammatory and profibrogenic mediators. PLoS One, 2013; 8(7): 69276.
3. Cassady, J. M., Zennie, T. M., Chae, Y. H., Ferin, M. A., Portuondo, N. E., Baird, W. M. Use of a mammalian cell culture benzo(a)pyrene metabolism assay for the detection of potential anticarcinogens from natural products: inhibition of metabolism by biochanin A, an isoflavone from Trifolium pratense L. *Cancer Res.*, 1988; 4822): 6257–6261.
4. Chen HQ, Zheng YJ, Li GH. Biochanin-A protects dopaminergic neurons against lipopolysaccharide-induced damage through inhibition of microglia activation and proinflammatory factors generation. Neuroscience Letters, 2007; 417: 112-117.
5. Da Silva, J., Pierrat, B., Mary, J.L., Lesslauer, W., Blockade of p38 mitogen-activated protein kinase pathway inhibits inducible nitric-oxide synthase expression in mouse astrocytes. J. Biol. Chem., 1997' 272: 28373–28380.
6. Das, A., Kole, L., Wang, L., Barrios, R., Moorthy, B., Jaiswal, A.K., BALT development and augmentation of hyperoxic lung injury in mice deficient in NQO1 and NQO2. Free. Radic. Biol. Med., 2006; 40: 1843–1856.
7. Heinonen, S., Wähälä, K., Adlercreutz, H. Identification of isoflavone metabolites dihydrodaidzein, dihydrogenistein, 6′-oh-o-dma, and cis-4-oh-equol in human urine by gas chromatography–mass spectroscopy using authentic reference compounds. *Anal. Biochem*, 1999; 274: 211–219.
8. Jain A, Lai JC, Bhushan A. Biochanin-A inhibits endothelial cell functions and proangiogenic pathways. Anticancer Drugs, 2015; 26(3): 323-330.
9. Lai, X., Li, Y., Gao, M. Biochanin A regulates the growth and migration of NSCLC through suppressing the VEGF/VEGFR2 signaling pathway. *Oncol. Res.*, 2018.
10. Liang, F., Cao, W., Huang, Y., Fang, Y., Cheng, Y., Pan, S., et al. Isoflavone biochanin A, a novel nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element activator, protects against oxidative damage in HepG2 cells. *Biofactors*, 2019; 1-12.
11. Lim, T. G., Kim, J. E., Jung, S. K., Li, Y., Bode, A. M., Park, J. S., et al. MLK3 is a direct target of biochanin A, which plays a role in solar UV-induced COX-2 expression in human keratinocytes. *Biochem. Pharmacol.* 2013; 86(7): 896–903.
12. Puthli, A., Tiwari, R., Mishra, K. P. Biochanin A enhances the radiotoxicity in colon tumor cells in vitro. *J. Environ. Pathol. Toxicol. Oncol*, 2013; 32(3): 189–203.
13. Sehdev V, Lai JC, Bhushan A. 2009. Biochanin-A modulates cell viability, invasion, and growth promoting signaling pathways in HER-2-positive breast cancer cells. Journal of Oncology, 2009 Article ID 121458, 10.
14. Sehm, T., Fan, Z., Weiss, R., Schwarz, M., Engelhorn, T., Hore, N., et al. The impact of dietary isoflavonoids on malignant brain tumors. *Cancer Med.*, 2014; 3(4): 865–877.
15. Szliszka E, Czuba ZP, Mertas A, Paradysz A, Krol W. The dietary isoflavone biochanin-A sensitizes prostate cancer cells to TRAIL-induced apoptosis. Urologic Oncology, 2013; 31(3): 331-342.
16. Vitale, D. C., Piazza, C., Melilli, B., Drago, F., Salomone, S. Isoflavones: estrogenic activity, biological effect and bioavailability. *Eur. J. Drug Metab. Pharmacokinet*, 2013; 38(1): 15–25.
17. Wang, Y., Man Gho, W., Chan, F. L., Chen, S., Leung, L. K. The red clover (Trifolium pratense) isoflavone biochanin A inhibits aromatase activity and expression. *Br. J. Nutr.*, 2008; 99(2): 303–310.